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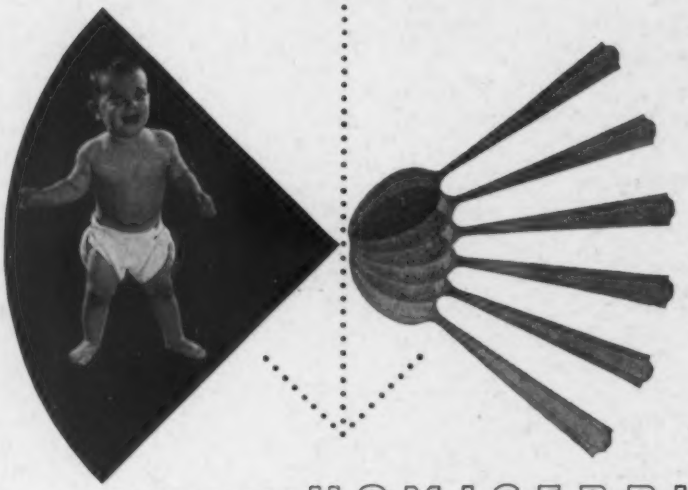

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The Journal of Pediatrics

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Original Communications

SOME PRACTICAL ASPECTS OF ALLERGY

SUSAN C. DEES, M.D.
DURHAM, N. C.

THE practical aspects of allergy are quite different for physician, parent, and patient. The physician is primarily interested in diagnosis and treatment. The parent and patient are concerned with immediate results of treatment, its execution, cost, and inconvenience, as well as the prognosis and possible complications of the disease.

The emphasis in this presentation will be on respiratory allergy, and some aspects of eczema and urticaria, since our experience with nearly three thousand allergic children seen in the Duke Hospital Pediatric Allergy Clinic in the past ten years shows these to be the most common problems.

Major allergy is present in at least 10 per cent of the general population, and an additional estimated 50 per cent may have minor allergy.[1] Asthma began before 10 years of age in at least one-third of adult asthmatics reported by Derbes and Engelhardt.[2] A tabulation of some of our personal experience with allergic children stresses even more the early age of onset (Table I). These observations emphasize the importance of major allergy as a pediatric problem. If time permitted a discussion of minor allergic symptoms in children we would find that allergy often accounts for much other illness as well.

The pediatrician has a unique advantage over a consulting allergist, in that he already knows the family history, the details of environment, the emotional factors, activities, infection, diet, and medication which the child has had since birth. He knows which children are unsupervised or overprotected, which households are chaotic and which ones run smoothly (Table II). This knowledge of nonspecific and possible allergic factors is considered vital information by the allergist, who acquires it only by laborious cross examination. The only thing the pediatrician lacks to become a good practical allergist is a little more information about the common allergens, and a reminder that allergic diseases vary greatly in severity. In mild allergy the onset of symptoms following exposure to an allergen is more delayed than in marked sensitivity and may require reinforcement by nonspecific factors.

From the Department of Pediatrics, Duke University Medical School, and the Duke University Hospital.

Presented before the Eastern Area Meeting, American Academy of Pediatrics, Philadelphia, Pa., March 30, 1950.

Certain basic foods, pollens, house dust, fungi, bacteria, and, rarely, drugs are the common allergens. To illustrate this the skin sensitivities in 100 asthmatic children are shown in Table III.

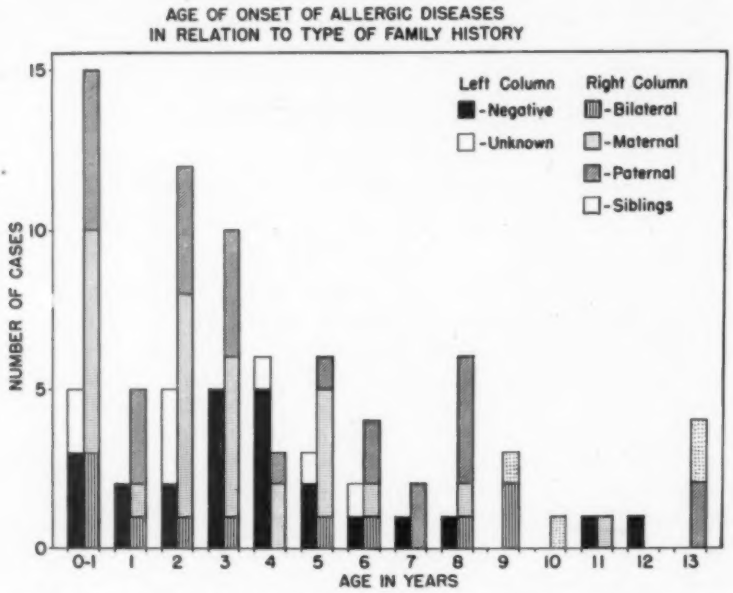

Table I.—Age of onset of allergic symptoms in 104 allergic children related to type of family history. Left column, negative or unknown family history. Right column, bilateral, maternal, paternal, or sibling history positive for allergy. Note onset before 8 years of age in 93 of 104 patients.

TABLE II. DIAGNOSTIC FEATURES OF ALLERGIC DISORDERS

1. Family history of allergy
2. Stereotyped symptomatology
3. Eosinophilia
4. Specific skin sensitivity
5. Relief of symptoms by
   a. Removal of allergen
   b. "Antiallergic" drugs

POLLENS

Pollen, to be of practical importance as a cause of allergy, must first of all be an irritant and be present in sufficient amounts to act as an air contaminant. This is true also of fungus spores. Only the plants which are wind pollinated produce sufficient pollen to fall into this class. The flowering plants cause trouble only when in very close proximity to the patient, as in a closed room or when actually handled. Pollen increases in the air during storms, has normal peaks at noon, and between midnight and dawn.

TABLE III. INTRADERMAL SKIN TESTS IN 100 ASTHMATIC CHILDREN

	POSITIVE	NEGATIVE	TOTAL PATIENTS	PERCENTAGE OF POSITIVE REACTORS	CONCENTRATION USED % VOL.
Dust	83	17	100	83	1:1,000
Pollen	77	19	96	80	1:1,000
Feathers	74	23	97	76	1:1,000
Chocolate	36	58	94	38	1:100
Milk	36	60	96	37	1:100 or 1:1,000
Cottonseed	35	62	97	36	1:1,000
Wheat	33	63	96	34	1:100 or 1:1,000
Vegetables	29	64	93	31	1:100
Egg	22	73	95	23	1:100 or 1:1,000
Orange	8	83	91	9	1:100
Bacteria	49	8	57	86	Variable
Fungi	27	11	38	71	1:100

What are the important pollens in the Southeastern United States, and when are they in the air? In general, trees pollinate in early spring, grasses from late spring to frost. Ragweed is the major pollen in the air from the first or second week of August to frost. It is important to realize that throughout most of the South there are only about two entirely pollen-free months. The details for any locality can be found in the pollen charts in texts on allergy or in brochures from commercial biological firms, who are prepared to furnish skin testing sets and adequate treatment mixtures on the basis of these tests (Table IV).

TABLE IV. COMMERCIAL SOURCES FOR ALLERGENS

Abbott Laboratories, North Chicago, Ill.
Arlington Chemical Co., Yonkers 1, N. Y.
C. G. Blatt & Co., Independence, Mo. (Dry Pollen).
Endo Products, Inc., Richmond Hill 18, N. Y. (House Dust).
Graham Laboratories, Dallas, Texas (Oleoresins).
Hollister-Stier Laboratories, Wilkinsburg, Pa.
Lederle Laboratories, Inc., Pearl River, N. J.
Parke, Davis & Co., Detroit, Mich.
Ross Pollen Laboratories, Oklahoma City 6, Okla.
Sharp & Sharp, Everett, Wash. (Dry Pollen).
Stemen Laboratories, Inc., Oklahoma City, Okla.
E. R. Squibb & Sons, New York 22, N. Y.
Wyeth Incorporated, Philadelphia 3, Pa.

Translated into the patient's terms this means that if a plant is prevalent in an area and wind pollinated little relief can be expected from destroying it in the immediate neighborhood. It also means that staying indoors after sundown, keeping bedroom windows closed at night, and avoiding evening automobile rides may greatly cut down pollen exposure. The doctor is often asked to help in the choice of a pollen-free vacation spot. If he recommends the beach, he should remind parents that the beach will be relatively pollen free only when the wind is from the ocean. Very few mountain resorts are still sufficiently forested to be the good havens from grass and weed pollen they once were. If the doctor suggests air conditioning at home, he should recommend that parents obtain expert advice from reputable air-conditioning engineers regarding the type of unit most efficient for the particular home. Air cleansing units

consisting of a simply installed window filter of glass wool with fan can be purchased at department or appliance stores for about $30.00. These remove considerable pollen, but do not give pollen-free air nor adequate cooling in hot weather. This can be accomplished to a degree by keeping ice or water in front of the fan.

Efficient individual room air-conditioning units cost about $300.00; an entire eight- to ten-room house can be air conditioned at present for about $1,500.00. These devices add to the pollen allergic's comfort, but do not completely remove all the pollen from the air. The various types of units have been investigated by impartial committees, improvements based on their recommendations are constantly in progress.[3] One disadvantage in all of the window filter types of unit is that the allergens within the room are not removed. This is partially accomplished by an electronic type of filter. These are available for about $600.00 to $700.00 for a household size unit.* They can be installed in any hot air-heated house or in a new house at the time of construction with other types of heating at little added cost. For patients sensitive to fungi, whose houses have damp basements, a dehumidifier electrically operated is now available.† This makes no claim to be fungicidal, but it is efficient in removing excessive moisture which encourages fungus growth. Attic fans are usually not suitable for pollen-sensitive persons since they increase the circulation of pollen in the house.

DUST

House dust is the most important inhalant allergen, one to which approximately 85 per cent of patients with respiratory allergy, and many with eczema, are sensitive. What is the house dust allergen? Nobody knows exactly, except that it is a protein substance which can be extracted from the aging conglomeration of dust from things in our houses. It is entirely different from outdoor dust, which is relatively inert allergenically.

Dust sensitivity may be controlled by removal of nonessential furnishings, by using dustproof covering for pillows, mattresses, upholstered furniture, or by rubber foam pillows and mattresses. Washed pine needles can be used as pillow or mattress stuffing, for insignificant cost. A new product "Dust-Seal,"‡ which is a water-oil emulsion spray, for coating fabrics and surfaces with a fine impervious film, is currently being suggested as a substitute for asceticism in furnishing a dust-free room. It has been in use too short a time to permit extensive evaluation, but so far shows promise of being a very helpful tool in certain homes where it is not practical or desirable to strip the rooms. The use of a steam vaporizer for several hours daily aids in controlling dust in bedrooms. Hot air heating systems without adequate filters or humidifying devices, with registers near patients' beds, are frequently responsible for failure of otherwise adequate dust precautions. Warm air circulators, or heating units from which

*Precipitron, Westinghouse Manufacturing Company, Hyde Park, Boston 36, Mass.
Trion Unit, Trion Company, 1000 Island Ave., McKees Rocks, Pa.
†Air Temp Unit, Air Temp Division, Chrysler Corporation.
‡L. S. Green Associates, 160 West 59th St., New York 19, N. Y.

there are fumes and smoke, are likewise irritating. Many mothers have found that simple coil or flat bed springs, which can easily be washed with a hose, are good for children's beds. Some children are comfortable on army cots, or air mattresses, which are inexpensive enough for nearly everyone. The various companies which make nonallergic bedding covers have brochures on dust precautions for patients which they will send gratis to physicians. Have any of you read carefully the details of these dust precautions? They sound easy until translated into the mother's terms, when they may mean an impossible work load, or the disintegration of an attractively and expensively decorated home. Can you imagine any mother carrying them out to the letter and having time or energy for any other household duties? The house dust allergen is important both immunologically and domestically in very different ways.

Horse hair and dander sensitivity, which used to be thought the stigma of the allergic person, seems no longer universal, except in farm children or those who ride a great deal. This does not mean we can omit tests for horse serum sensitivity prior to administering therapeutic sera to allergics, but in my experience this must be far less frequent now than it was as much as fifteen years ago.

Some allergists forbid their allergic patients to have any furry household pets. I have seen many children who are exquisitely sensitive to cats and rabbits, with severe symptoms at the slightest exposure to them. I can recall no child in whom I have ever seen such clear-cut symptoms from contact with dogs, in spite of many marked skin test reactions to dog hair. I have been responsible for the temporary or permanent removal of dogs from many homes. In only a very few instances was this followed by incontestable improvement, nor did symptoms recur when a dog was returned to the home. From my own observations, therefore, I do not think dog sensitivity is either as common or as severe as that to many other animal allergens.

FOODS

Foods are important allergens, although allergists and pediatricians do not agree among themselves as to their relative significance in various clinical allergies. It is probably safe to say that they are of less importance in most children with respiratory allergy than are airborne allergens, regardless of the age of the child. The actual foods which lead the list will vary somewhat with different observers. Most people will agree that cow's milk, eggs, cereals, white potato. orange, and chocolate are the most common. In India the cow is sacred; in this country so far as children are concerned, cow's milk is sacred. I feel sure if our traditional diets consisted of whale milk, cormorant eggs, persimmons, and betel nuts that these would take first place. People become sensitive to the things to which they have repeated, prolonged, and intimate exposure, and our food sensitivities reflect very closely our eating habits. The rotation diets popularized by Rinkel,[4] stemming from years of observation by Rowe,[5] Vaughan,[6] and Randolph,[7] seem a most sensible program particularly for allergic or potentially allergic children.

When basic foods must be eliminated for a brief trial, or for a long period, special diets must be provided for the patient. A partial list of many such diets is shown in Table V, which helps to provide substitutes for common dishes. These details are mentioned because most of us are unimaginative in our eating habits, and a few suggestions will help keep meals from being unappetizing, and help children to actually take the suggested elimination diet.

TABLE V. ELIMINATION DIETS AND RECIPES

Rowe, A. H.: Elimination Diets and Patient's Allergies, Philadelphia, 1944, Lea & Febiger. (Menus only—J. W. Stacey, Inc., Flood Bldg., San Francisco, Calif.)
Vaughan, Warren: Practice of Allergy, St. Louis, 1940, The C. V. Mosby Co.
Haas, Myra May, and Shaffer, Nathan: Recipes and Menus for Allergics, New York, 1940, Dodd, Mead & Co., Inc.
Alvarez, W. C.: Help Us to Help You When You Have a Food Allergy, New York, 1941, Harper & Brothers.
American Dietetic Association, 620 N. Michigan Ave., Chicago 11, Ill., "Allergy Recipes" 1944-1945.
Ralston Purina Company, St. Louis, Mo., "Allergy Diets."
U. S. Department of Agriculture, Bureau Home Economics, "Recipes for Baked Products for Those Who Cannot Use Wheat, Milk, Eggs."
Good Housekeeping Publishing Co., "Help for Allergics."
Chicago Dietetics Supply Co., "Wheat, Milk, Egg Free Recipes."
Quaker Oats Company, Research Laboratory, Chicago, Ill.

In dealing with allergic children it is important not to restrict a diet nor to cast suspicion on foods without excellent reasons, since some mothers and children will use this as the starting point for major food phobias.

Along with detection of common allergens we have suggested some means of avoidance or hyposensitization. The latter is a technique for raising the patient's tolerance to things which he cannot effectively avoid. This has proved a most helpful adjunct to treatment of pollen, inhalant, fungus, and occasionally bacterial sensitivity. It is surprisingly well tolerated by even very young children, and as nearly as one can evaluate such things, which must be used in conjunction with other types of treatment, it is highly successful.

TREATMENT

While we have been discussing the commonplace aspects of allergy concerned with etiologic diagnosis, the pediatrician and the parents are asking, and the patient is demanding, "What can you do for symptoms right now?" Many allergic children will at some time have acute episodes which demand emergency measures. These are usually severe asthma or status asthmaticus, severe generalized eczema, angioneurotic edema, or urticaria, or anaphylactoid reactions due to various causes. Every physician who treats children should systematize his preferred routine, or should adopt one such as outlined by Glaser,[8] Ratner,[9] Stoesser,[10] Davison,[11] and others so that his associates can function smoothly and rapidly with him in executing orders for oxygen, intravenous fluids, steam, chemotherapy, antispasmodics, antihistaminics, and other supportive measures. Reassurance, sedation, hydration, and control of infection are of paramount im-

portance in these circumstances. It is unnecessary here to detail dosages of drugs, but some scheme such as that shown in Tables VI to VIII may serve as a skeleton to be modified as indicated for each patient.

TABLE VI. ASTHMA THERAPY

1. Complete bed rest, enemas, oxygen therapy.
2. Fluids: oral, intravenous, subcutaneous.
3. Sedation: phenobarbital sodium, Seconal, Nembutal, Demerol, chloral hydrate.
4. Aminophyllin: intravenously 3 mg. per pound, in 10 per cent glucose, 100 to 150 c.c.; rectally 0.1 to 0.25 Gm. suppository or instillation.
5. Epinephrine: 1:1,000, 0.1 to 0.2 c.c. every 20 minutes for 4 to 6 doses. Rest 2 hours. Repeat if necessary.
6. Epinephrine in oil: 1:500, 0.3 to 1 c.c. intramuscularly.
7. Norisodrine, Isuprel, Vaponefrin, or epinephrine 1:100 by nebulizer once every 2 to 4 hours, preferably with O_2 (only in selected cases).
8. Helium, 80 per cent mixed with oxygen 20 per cent where closed mask is tolerated.
9. Expectorants: potassium iodide, 3 to 10 Gtt.; syrup hydriodic acid, 2 to 5 c.c.; ammonium chloride, 0.1 Gm. t.i.d.
10. Retention enemas. (Older children) Aminophyllin 0.25 to 0.5 Gm. in 1 to 2 oz. warm water. May be combined with 10 c.c. of 10 per cent chloral hydrate and given 2 to 3 times daily. Ether, 30 to 60 c.c. in equal amount of olive oil per rectum.
11. Bronchoscopy.
12. Antibiotics or chemotherapy.

TABLE VII. SYMPTOMATIC TREATMENT FOR SEVERE URTICARIA

a. Saline cathartics and enemas.
b. Fast for 18 to 24 hours (glucose).
c. Liquid diet for next 24 hours, fruit juice, tea, milk.
d. Starch and soda baths.
e. Antipruritic lotions and dusting powders (talc + ½ per cent menthol).
f. Antihistaminics in adequate dosage—Benadryl 2 to 4 mg. per pound per 24 hours in 4 or 5 doses. Pyribenzamine or others in appropriate dosage. Benadryl intravenous, ⅓ to ½ single oral dose.
g. Epinephrine hcl 1:1,000 (h) 0.1 c.c. q. 15. min., 4 to 6 times, rest 1 to 2 hours and repeat.
h. Butanefrine 1:500, 0.2 c.c. as epinephrine above.
i. Ephedrine or ephedrine-like compounds (Propadrine, etc.).
j. Sedation—phenobarbital, pentobarbital sodium, chloral hydrate 10 per cent, 1 to 10 c.c.
k. Calcium gluconate 10 per cent solution, 3 to 10 c.c. intravenously.
l. Autohemotherapy 10 to 20 c.c. intramuscularly.

We might review some familiar practical points and some threadbare do's and don'ts. The physician must be meticulous in his attention to every detail of the patient's program. Hospitalize the acutely ill allergic child whenever this is practical. This gets him away from probable allergens, and facilitates special treatment. Do not leave him alone until his acute symptoms are completely controlled. Check all equipment such as oxygen tanks, tents, etc., to be sure they are actually delivering the desired amount of oxygen at proper temperature and humidity; make sure that adequate steam is present. Do not rely on the oral route for fluids in the first few hours of treatment. Make sure no obviously allergenic pillows and so forth are in the patient's bed or room. Check all foods and drugs ordered with patient's known or possible allergens.

TABLE VIII. ECZEMA THERAPY

Acute Stage—Erythematous, vesicular, weeping, edematous lesions.

1. Protection from skin irritants:
   Wool Nylon Plastics Dust
   Silk Rayon Soap Feathers
2. Prevention of scratching—restraints.
3. Sedation—antipruritics:
   Barbiturates Antihistaminics
   Chloralhydrate
4. Cleansing skin and scalp with:
   Bland oil Starch baths $KMnO_4$
   Soda water Saline Detergents
5. Protection and soothing skin with compresses:
   Saline $KMnO_4$ 1:6000
   Chloresium Burow's Solution 1:40
   Tyrothricin Domeboro tablets 1:1 qt. water
6. Skin antisepsis:
   Colorless Tr. Zephiran 1:1,000
   Gentian violet 1 per cent aqueous or alcoholic
   Castellani's paint
7. Bland antipruritic lotions:
   Calamine liniment or lotion
   Shake lotion (ZnO_2, talc, glycerin, water)
   Liquor carbonis detergens 5 per cent in shake lotion
   Burow's emulsion with menthol ¼ per cent in phenol 1 per cent
   Benzocaine 3 to 10 per cent
8. Bland ointment:
   ZnO_2 paste Petrolatum
   Chloresium Cold cream
   Boric Acid Vanishing cream
   Rosen's ointment Antihistaminic ointment
9. Mild skin stimulants:
   Liquor carbonis detergens 3 to 10 per cent
   Crude or distilled tar 3 per cent
   Ichthyol 3 per cent
   Oil of cade 5 to 10 per cent
   Resorcinol monoacetate 5 per cent
   Naftalan 3 to 5 per cent

   May add:
   Salicylic acid 1 to 3 per cent Sulfur 1 to 3 per cent
   Ammoniated mercury 2 to 5 per cent

   Proprietary ointments:
   Mazon Tar alba
   Pragmatar Supertah

At all times respect the patient's or parent's suspicions regarding things which are not tolerated, regardless of how far-fetched they may seem, but particularly during acute allergic episodes. The medical literature contains too many reports of severe reactions to drugs, for example, which have been administered in spite of a patient's unheeded warnings. The medicolegal aspects of this are obvious.

Use adequate doses of drugs with which you are perfectly familiar, so that their pharmacologic effect can be anticipated. Do not try out the latest remedy on an acutely ill child until you are certain that it is proved superior to accepted treatment. Do not use routes of administration in which dose and rate of absorption are uncertain. One of the pitfalls in management of allergic emergencies is overtreatment. If the physician becomes impatient with the apparent results of his program, he is likely to find himself ordering one drug after another to counteract some of the effects of his previous prescriptions.

In severe eczema we are less likely to overmedicate, but our impatience frequently leads us to abandon a rational program of treatment before we have given it an adequate trial. I have found it helpful in my thinking about eczema and in explaining the problem to parents, to ask myself and them, how long we would expect for the skin to heal, if it were this badly damaged by a hot water burn. Then we both realize that it will not heal overnight. We also know that the burn is over quickly, while in eczema the damaging agent and scratching may still be adding trauma to the skin. A uniformly successful program of treatment for severe eczema has not yet been devised. There are occasional amazing results, but no one basic plan which always works. On what can we count, then, other than the healing powers of the passage of time? The latest wonder drugs, ACTH or cortisone? Possibly. On diet? Important, but it is not the entire solution for treatment for most infantile eczema. The diet in acute severe eczema must contain adequate amounts of all the essential nutritional requirements even though limited in variety of foods. Every baby I have ever seen with extremely severe eczema has had crises with clinical and chemical evidence of abnormal metabolism. They have had edema, acidosis, dehydration, or avitaminosis, low plasma proteins, reversed A/G ratio, abnormal electrolyte patterns, and blood fatty acid levels.[12, 13] When oral unsaturated fatty acids as Soyola, lard, corn, or linseed oil are ordered, they must be used for weeks or even months for full effect. The blood fatty acid levels are slowly altered by oral administration, although they may rise quickly after acute infection or after application of coal tar to the skin.

If the child is being treated at home, explicit written instructions, reinforced with demonstrations of each procedure, are imperative for good results. We all consider protection of the skin from further trauma of major importance. This we attempt to accomplish by avoiding external irritants, by sedation, protective creams, lotions, dressings, compresses, baths, and restraints. The traditional practice of forcible physical restraint of hospitalized eczematous infants may be open to criticism on psychological grounds.[14] It seems possible that we might enrage a baby sufficiently by restraints to produce or intensify an "alarm reaction." If this is part of the basic allergic process as suggested by Selye,[15] some less medieval and more efficient technique for protecting the skin is urgently needed.

The acute infection of the skin which often complicates severe eczema must be treated vigorously and adequately. If this is not done the patient may develop drug sensitivity, or the organisms may become phenomenally resistant to chemotherapy, or insensitive organisms such as *Bacillus proteus*, *Pseudomonas aeruginosa*, or fungi may have replaced the original flora as a result of inadequate topical treatment.

The treatment of acute allergic conditions does not include direct diagnostic tests of any type. Acute asthma, edema, or eczema are as severe illnesses as pneumonia or diarrhea, and the patient should be disturbed as little as possible. In addition, tests done at such times are unreliable, and must be confirmed at a later date. Even more important is the very real danger of pro-

ducing constitutional reactions at this time. The physician must not yield to his curiosity, nor to parent's urging, to start tests with the first easy breaths or bit of clear skin.

We all are careful not to vaccinate eczematous infants for smallpox because of the danger of eczema vaccinatum. The eczematous child should also be kept away from any recently vaccinated person.

Smallpox vaccination in eczema is the only routine immunization which is contraindicated because of allergy. Many physicians hesitate to carry out the usual injections for pertussis, diphtheria, tetanus, and typhoid in allergic children for fear of reactions, even though highly purified products from which reactions are negligible are now available.[16] If one is apprehensive he can always give a small fraction of the usual dose as a test dose and complete the series with small divided doses. As a precaution, even though one will probably never need it, Adrenalin should be immediately available, and the patient should be unobtrusively observed for at least one-half hour after injection. Those of us who have sat up all night giving tetanus or diphtheria antitoxin to an allergic child, who is sensitive to horse serum, feel very strongly that they need prophylactic immunization even more than normal children.

Success in managing chronic allergic problems in children depends as much, if not more, on the recognition and control of the nonspecific factors, as on the purely allergic features. We have already stressed the importance of infection. Parents repeatedly state that "change in the weather, getting feet wet, having a shampoo, are the only things which make my child worse." Experimental work on the effect of heating, chilling, and humidity on allergic reactions gives some explanation for this observation.[17] In practical terms this means that allergic children should be protected against exposures by adequate clothing, particularly for head and legs. Their bedrooms must be kept at an even temperature. The heat and cold exercises devised years ago by Duke,[18] consisting of immersion of hands in warm then cool water for one or two minutes, with daily increase in temperature difference, can be carried out by even the youngest child. In addition to improved tolerance of temperature change, this procedure has a good psychological effect on parents, for whom a definite program is substituted for worry and nagging about exposure, and for the child who can look forward to some emancipation from bundling.

In children with asthma, breathing exercises are a most helpful form of treatment. Here again one couples a psychological with a physiological approach. The exercises we use are modified from those described by the London County Council.[19] They not only increase a child's vital capacity by several hundred cubic centimeters, and improve his posture, but they may give him a way of aborting an attack himself without using any medication. This sense of control or power over an asthmatic attack is invaluable. These exercises cannot be well mastered by children less than 5 years of age. Modifications of this technique for encouraging complete expiration which are suitable for little children are blowing balloons, blowing through straws, blowing water from one bottle to another. People forget exercises easily, both in doing them correctly and at all, so they must be reviewed frequently.

Psychosomatic problems are most important nonspecific factors in producing and modifying allergic symptoms. These have been presented in many authoritative studies.[20, 21] In my own experience I have not yet encountered any child in whom psychogenic factors were the sole basis for allergy, but I have seen a great many children in whom they overshadowed protein sensitivity in actually producing allergic attacks.[22] Pediatrician and parents are keenly aware of their importance and often find that simple measures and changes in attitudes toward the child will help to correct them. At times they can only be unravelled and adjusted by skillful psychiatric guidance.

Parents are vitally interested in one other aspect of allergic diagnosis and treatment, its cost. The emphasis in this presentation has been upon the simple things which can be done effectively by any pediatrician and mother, without any special equipment, or elaborate testing. Using this approach, the cost of diagnosing and treating allergy is very low. Should these measures prove incomplete, then special skin tests, passive transfer tests, x-rays, hyposensitization, and various other procedures will probably require the assistance of an allergist and other consultants. The costs of these studies are comparable to other consultant fees and special examinations and vary with the locality. In my opinion most parents would be delighted to give the simple conservative approach a reasonable trial, for other reasons in addition to the economic, if pediatricians would not imply a complete bewilderment about the management of allergic complaints. Parents translate this to mean that their child's problem is hopeless, and they then lose faith in the doctor's suggestions regarding everyday environmental factors. They frantically think of a drastic climate change, or insist upon a battery of skin tests from an allergist. If the pediatrician would only capitalize on the faith parents have in him, on his knowledge of the allergic child and his surroundings, and add to this some of the more practical features of allergic diagnosis and treatment, he could recognize allergy much earlier, and treat it much more effectively than is often the case today.

The practical aspects of allergy are varied, as can be seen by our ranging from immunology to pharmacology, from pollens to recipes, from psychosomatics to house furnishings. We cannot hope to answer most of the questions we originally posed regarding allergy until we understand and can favorably control its fundamental processes. When we have this knowledge we will reach the millenium when all drugs, ointments, "shots," dust precautions, and diets can be forgotten. Until that day, we as pediatricians can do much, by simple measures, to keep allergic children healthy and happy.

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RELATION OF HYALURONIDASE TO SALICYLATES AND RHEUMATIC FEVER

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THE purpose of this paper is to present studies concerning the cutaneous spread of Evans blue dye, T-1824, with hyaluronidase in rheumatic fever patients as compared to nonrheumatic subjects, and the effects of salicylate and succinate therapy on this spreading factor process. Although the causative agent of rheumatic fever is assumed by many to be the hemolytic streptococcus, extremely little is definitely known as to the exact mechanism that the streptococcus produces the diffuse mesenchymal rheumatic pathology.[1, 2] Also the therapeutic action of salicylates in rheumatic fever, although long utilized by many, still remains a pharmacological enigma.[3] Our studies were performed to further investigate the recent speculations,[4-7] that the streptococcal enzyme hyaluronidase may be the specific agent in the pathogenesis of rheumatic fever and that it is directly inhibited by salicylates.

Hyaluronidase was first reported as a spreading factor by Duran-Reynals[8] and McClean,[9] present in testicular extract, and since obtained also from leech extracts, snake venoms, and many strains of bacteria as streptococci, staphylococci, pneumococci, and *Clostridium welchii*.[7] Chain and Duthie[10] identified this spreading factor as hyaluronidase, a mucolytic enzyme which acts on and is depolymerized by hydrolysis hyaluronic acid,[7, 11-13] a mucopolysaccharide gel shown to be present in the skin, synovial fluid, umbilical cord, vitreous humor, and widely distributed as the cementing ground substance of connective tissue. By action of hydrolysis by hyaluronidase, the viscosity of the hyaluronate gel is reduced, thereby facilitating fluid diffusion, which is the basis of the cutaneous dye diffusion biological assay method of the hyaluronidase enzyme and the hyaluronic acid substrate system first established by Humphrey.[14]

In 1946, Guerra[4-6] proposed the new stimulating concepts that the mechanism of rheumatic fever involves the degradation of hyaluronic acid by hyaluronidase and that the therapeutic efficacy of sodium salicylate is explained by its inhibitory action on the mucolytic enzyme, hyaluronidase. In his experiments, when hyaluronidase of either testicular or streptococcal origin was intracutaneously injected with Evans blue dye as an indicator in a total volume of 0.5 c.c., there was a greater area of dye diffusion in the active and convalescent rheumatic patients as compared with normal subjects. In the rheumatic patients, the hyaluronidase and dye skin tests were generally accompanied by moderate local inflammatory reactions, which were probably due to

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impurities in the enzyme product being tested. With sodium salicylate therapy, the increased spread of dye with hyaluronidase was almost completely neutralized to that of a normal subject. In normal adults and children, and also in albino rabbits, the administration of sodium salicylate effected a 50 to 80 per cent reduction of the cutaneous spread of dye with hyaluronidase, and a 20 per cent reduction in the spread of the indicator dye without the enzyme.

The rationale of the suggested concepts of Guerra[4-6] and Myers[7] regarding the pathogenesis of rheumatic fever and the mechanism of salicylate action is based on the following: rheumatic fever is a disease of the connective tissue mesenchyma; an important constituent of connective tissue is hyaluronic acid which is susceptible to the enzymic action of hyaluronidase; hemolytic streptococci produce this hyaluronidase enzyme;[15] and hyaluronidase causes in the skin of rheumatic patients increased spreading reactions which may be inhibited by salicylates.

Within the past four years, many investigators have attempted to produce in vivo and in vitro experiments that would help clarify the relation of hyaluronidase to salicylates and rheumatic fever, but as yet the conclusions are indecisive and still await further accumulative data.

Although Dorfman and collaborators[16] have been able to demonstrate in vivo definite inhibition of cutaneous spreading activity of hyaluronidase in albino rabbits with oral and intravenous administration of salicylates, they found that in vitro using viscosimetric methods that salicylates were incapable of exhibiting hyaluronidase inhibition unless considerably higher than normal in vivo concentrations were used as 1 to 2 Gm. per cent. It has been shown that salicylates at relatively high concentrations cause a reversible denaturation of biologically active proteins.[17, 18] Others,[19-21] using various in vitro methods, have been unable to demonstrate any inhibitory action of sodium salicylate on hyaluronidase of either testicular or bacterial origin. Lowenthal and Gagnon found that gentisic acid, a metabolic product of salicylic acid, produced no in vitro decrease of hyaluronidase activity, but that carboxy-p-benzoquinone, the next oxidation product of gentisic acid, effected a significant inhibition.

In regard to the presence of hyaluronidase inhibiting substances in sera of rheumatic fever patients, as compared with normal persons, some recent reports suggest a significant difference. Wilson and her associates[22] and also Fulton and his co-workers[21] report no significant difference in degree of inhibition of hyaluronidase of bovine origin by sera of normal children and patients with rheumatic fever. However, others, Friou,[23] Quinn,[24] and Harris,[25] have been able to demonstrate moderately significant higher antihyaluronidase titers against the enzyme derived from streptococcal origin in sera of patients with rheumatic fever as compared to sera of normal subjects and patients with uncomplicated streptococcal infections. Recently Good and Glick,[26] using bovine testicular hyaluronidase, found significant elevation of hyaluronidase antibody or inhibitor in sera of active rheumatic fever patients.

By means of intradermal injections with a dye indicator, Harris and Friedman[27] presented data recently which gave no evidence of increased sus-

ceptibility of the skin of rheumatic subjects to streptococcal spreading factor. In their experiments, the streptococcal hyaluronidase enzyme with an injecting volume of 0.05 c.c. generally produced minimal cutaneous inflammatory reactions. The present study was undertaken to further investigate and possibly corroborate the findings of others in regard to cutaneous dye diffusions tests.

METHOD AND MATERIAL

The rheumatic patients were studied at the Crawford Allen Memorial, North Kingston, R. I. In regard to the degree of rheumatic activity of the twenty-two children tested, four patients had definite clinical and laboratory evidence of active rheumatic fever and eighteen patients were in an inactive state convalescing for one to nine months following a proved rheumatic attack. As the active rheumatic patients numbered too few to be considered a separate group, they were considered as being in the same group statistically as the convalescing inactive rheumatic patients. Actually, the results of the active and inactive rheumatic groups were calculated separately, and no significant differences were noted, but no speculation can be made concerning this similarity because of the extremely small number of active rheumatic patients. The twenty-two children which served as a nonrheumatic control group were studied in the Children's Division, Sea View Hospital, Staten Island, N. Y. They were all patients with arrested primary pulmonary tuberculosis ready for discharge with negative physical findings and normal sedimentation rates and no recent history of upper respiratory infection. The patients in both the inactive rheumatic and nonrheumatic series, with an average age of 8 and 9 years, respectively, were white, with equal male and female sex distribution.

The method used to study the relation of hyaluronidase to salicylate and succinate therapy and rheumatic fever consisted of injecting intradermally an indicator dye with and without the spreading factor hyaluronidase, and then measuring the cutaneous dye diffusion area after a one- and two-hour interval.

The indicator dye used was Evans blue dye, T-1824,* 0.45 per cent concentration supplied in 5 c.c. ampules. T-1824, the same dye used by others[4-6, 14] in similar experiments, is a nontoxic intravital dye which actually stains the tissue, thereby rendering an easily discernible and definite demarcation of the dye diffusion area. In almost all cases the blue discoloration of the skin disappeared very gradually within a three-month period.

The spreading enzyme used was Alidase,† a highly purified brand of hyaluronidase derived of bovine testicular origin and supplied for investigational purposes only as 100 μg of dry sterile enzyme per vial. For all tests, the hyaluronidase produce was of the same batch and lot number. The high purity of the enzyme product was verified by the complete absence of any cutaneous inflammatory erythema or edema following the dye-enzyme injec-

*Supplied by Warner Institute for Therapeutic Research, New York, N. Y.

†Alidase is the commercial hyaluronidase product which was supplied through the courtesy of Dr. Irwin C. Winter, director of clinical research, G. D. Searle & Co., Chicago 80.

tions, a factor of significance, as accompanying inflammatory reactions affect to a fair degree the normal interstitial spreading process.[28] By an in vitro viscosimetric method of assay, 1 μg of dry enzyme material was equivalent to 1.25 viscosity units.[29] The concentration of hyaluronidase solution which was injected was 1 μg per 0.2 c.c. which was always prepared the day of skin testing.

The total volume of each intradermal injection was 0.2 c.c. to conform with standardization of previous investigators,[14, 28] and was administered *with a 1.0 c.c. tuberculin syringe* and a No. 26 gauge needle, always on the upper third of the inner aspect of the forearm. At simultaneous times, each patient received an experimental 0.2 c.c. injection consisting of 0.1 c.c. of dye T-1824, 0.45 per cent in water, plus 0.1 c.c. of 1 μg of hyaluronidase in isotonic saline, and a 0.2 c.c. control injection on the opposite forearm consisting of 0.1 c.c. of dye T-1824 plus 0.1 c.c. isotonic saline. Each subject in the nonrheumatic and inactive rheumatic fever groups received the experimental and the control injections at three separate times under the following conditions: (1) no therapy, (2) on sodium salicylate therapy, and (3) on succinate therapy.

Careful measurements of the cutaneous areas of dye diffusion were taken at one and two hours after each pair of injections. The area of discoloration was calculated in square millimeters utilizing the formula expressing the area of an ellipse.

$$A = \frac{\pi Dd}{4}$$

where D, in millimeters, represents the major diameter axis of the diffusion area, and d, also in millimeters, is the minor diameter axis perpendicular to D.

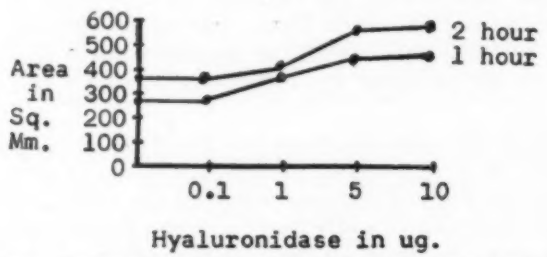

Chart 1.—Mean areas of dye diffusion in three normal nonrheumatic patients at one and two hours with increasing amounts of hyaluronidase in a constant volume of 0.2 c.c. per injection.

RESULTS

Preliminary studies were performed initially on three nonrheumatic normal children to determine the smallest amount of hyaluronidase enzyme that would produce a significant increase of dye spread as compared to dye injections with no enzyme. With a constant total volume of 0.2 c.c. per intradermal injection, consisting of 0.1 c.c. of dye T-1824 plus 0.1 c.c. of varying amounts of enzyme in saline, the area of dye diffusion varied with the amount of hyaluronidase in

a typical sigmoid curve[28] fashion as shown in Chart 1. From these studies, the threshold value of 1 μg of hyaluronidase per 0.2 c.c. injection was chosen for the entire study with the reasoning that this smallest amount of hyaluronidase causing a significant increase of dye spread would be most readily inhibited in action by the future administration of possible antihyaluronidase drugs as salicylates.

In all dye diffusion skin tests, area measurements were taken at the end of one and two hours. However, since the one-hour readings showed a slightly greater difference between comparison groups, only the one-hour readings are reported in the accompanying tables.

TABLE I. SUMMARY OF MEAN DYE DIFFUSION AREAS IN SQUARE MILLIMETERS AFTER ONE HOUR WITH CORRESPONDING COEFFICIENTS OF VARIATION OF NONRHEUMATIC AND INACTIVE RHEUMATIC GROUPS ON NO THERAPY, SALICYLATE THERAPY, AND SUCCINATE THERAPY

	DYE INJECTIONS WITH NO HYALURONIDASE			DYE INJECTIONS WITH HYALURONIDASE		
	THERAPY			THERAPY		
	NONE	SALICYLATE	SUCCINATE	NONE	SALICYLATE	SUCCINATE
Nonrheumatic	264	217	214	384	267	307
C. V.* in per cent	±27	±34	±22	±28	±32	±29
Inactive rheumatic	279	264	291	450	453	454
C. V. in per cent	±30	±35	±33	±33	±32	±34

*C. V. = coefficient of variation.

Included in Table I are the calculated mean dye diffusion areas in square millimeters with each coefficient of variation expressed in per cent of all the injections performed on all the patients. The C. V. (coefficient of variation) in per cent represents the ratio of the standard deviation of the mean to the mean times one hundred. The nonrheumatic subjects who received dye injections with and without the hyaluronidase enzyme under three conditions, no therapy, salicylate therapy, and succinate therapy numbered 22, 18, and 21

TABLE II. COMPARISON OF MEAN DYE DIFFUSION AREAS IN SQUARE MILLIMETERS AFTER ONE HOUR BETWEEN NONRHEUMATIC AND INACTIVE RHEUMATIC GROUPS

	A	B	C
	DYE INJECTIONS		PER CENT INCREASE B TO A
	NO HYALURONIDASE	WITH HYALURONIDASE	
Nonrheumatic	264	384	45.4
Inactive rheumatic	279	450	61.2

TABLE III. COMPARISON OF MEAN DYE DIFFUSION AREAS IN SQUARE MILLIMETERS AFTER ONE HOUR BETWEEN NONRHEUMATIC AND INACTIVE RHEUMATIC GROUPS

	A	B	C
	NONRHEUMATIC	INACTIVE RHEUMATIC	PER CENT INCREASE B TO A
Dye injections with no hyaluronidase	264	279	5.6
Dye injections with hyaluronidase	384	450	17.1

patients, respectively, while the inactive rheumatic fever patients, receiving similar injections under the same conditions, numbered 22, 19, and 16, respectively.

Graphically, the summary of all the results are depicted in Chart 2; however Tables II and III show the actual numerical and percentage change in the comparison of the mean dye diffusion areas with and without hyaluronidase of the inactive and nonrheumatic groups. When these tests were performed, no drug therapy was being administered to the patients. In Table II it is shown that in the nonrheumatic subjects the enzyme hyaluronidase caused a 45.4 per cent increase in the area of dye diffusion, while in the inactive rheumatic fever patients, the enzyme effected a 61.2 per cent increase. Both percentage increases are statistically significant.

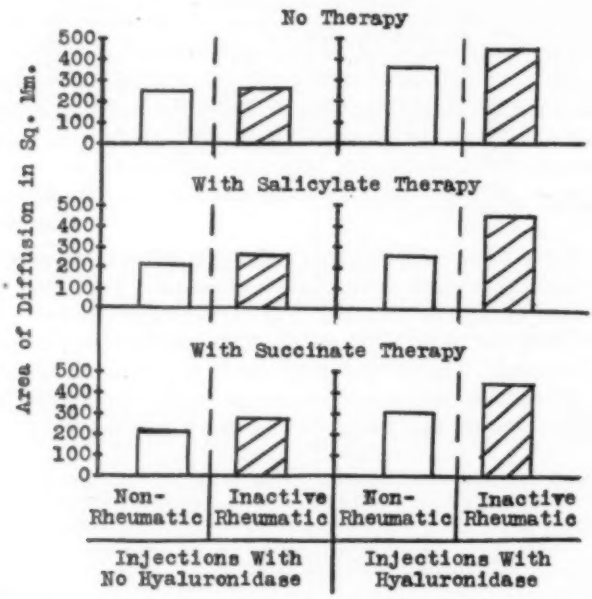

Chart 2.—Mean areas of dye diffusion in square millimeters at end of one hour caused by injections with and without 1 μg of hyaluronidase in a 0.2 c.c. dye-saline mixture in nonrheumatic and inactive rheumatic fever patients on no therapy, salicylate therapy, and succinate therapy.

Table III shows that hyaluronidase induced a 17.1 per cent greater spread of the dye in the inactive rheumatic patients as compared to the nonrheumatic subjects. This figure of 17.1 per cent is shown to be a statistically significant difference, while the 5.6 per cent difference of dye spread without hyaluronidase between the two groups is calculated to be not significant.

It should be mentioned at this time that the preliminary pilot tests on the normal subjects and all the dye tests on the inactive rheumatic fever group

were performed first, and five months later the tests on the nonrheumatic group were completed. By comparing the mean area of dye diffusion with hyaluronidase in the early preliminary studies on normal patients, and the later studies on the nonrheumatics, which were 372 and 384 sq. mm., respectively, the potency of the lot of hyaluronidase enzyme was considered to have remained unchanged during the entire study.

The relationship of sodium salicylate to the in vivo dye diffusion spreading was studied in an attempt to further investigation on the correlation of the antirheumatic drug to the hyaluronidase enzyme and hyaluronic acid substrate system. Approximately one week after the dye diffusion tests, with and without hyaluronidase, were performed on the nonrheumatic and the inactive rheumatic patients, exactly similar dye injections were again performed with all subjects maintained on sodium salicylate. Sodium salicylate was administered by mouth every four hours for twenty-four hours prior to testing in amounts equivalent to 1 gr. per pound of body weight per day. At the time of the one-hour dye diffusion area reading, blood was drawn from each patient to determine the salicylate level by the Brodie method.[30] The mean salicylate levels of the nonrheumatic and inactive rheumatic fever patients were 28.5 and 31.0 mg. per 100 c.c., respectively.

TABLE IV. EFFECT OF SODIUM SALICYLATE ON THE MEAN DYE DIFFUSION AREAS IN SQUARE MILLIMETERS AFTER ONE HOUR IN NONRHEUMATIC AND INACTIVE RHEUMATIC PATIENTS

	A	B	C	D	E	F
	DYE INJECTIONS WITH NO HYALURONIDASE			DYE INJECTIONS WITH HYALURONIDASE		
	NO THERAPY	SALICYLATE THERAPY	PER CENT DECREASE B TO A	NO THERAPY	SALICYLATE THERAPY	PER CENT DECREASE E TO D
Nonrheumatic	264	217	17.8	384	267	30.4
Inactive rheumatic	279	264	5.3	450	453	0

The calculated mean dye diffusion areas at one hour in Table IV reveal that the administration of sodium salicylate had no significant inhibitory effect on the cutaneous spread of dye with and without the enzyme in the inactive convalescing rheumatic subjects. However, in the nonrheumatic subjects, salicylate administration resulted in a 17.8 per cent decrease in the spread of the indicator dye without hyaluronidase, and a 30.4 per cent decrease of the dye spread with hyaluronidase. Both of these inhibition percentages are calculated to be statistically significant.

As it has been claimed[31] that Subenon,* a calcium double salt of benzoic acid and succinic acid benzyl ester, is equally or even more effective as an antirheumatic therapeutic agent than the allied salicylate drugs, similar in vivo cutaneous dye diffusion tests were performed with the patients on therapeutic doses of this succinate compound. Twenty-four hours prior to the time of dye injections and readings, all patients received Subenon by mouth every four hours in amounts equal to 1 gr. per pound of body weight per day.

*Obtained through the courtesy of Seydel Chemical Co., Jersey City, N. J.

TABLE V. EFFECT OF SUCCINATE THERAPY ON THE MEAN DYE DIFFUSION AREAS IN SQUARE MILLIMETERS AFTER ONE HOUR IN NONRHEUMATIC AND INACTIVE RHEUMATIC PATIENTS

	A	B	C	D	E	F
	DYE INJECTIONS WITH NO HYALURONIDASE		PER CENT DECREASE B TO A	DYE INJECTIONS WITH HYALURONIDASE		PER CENT DECREASE E TO D
	NO THERAPY	SUCCINATE THERAPY		NO THERAPY	SUCCINATE THERAPY	
Nonrheumatic	264	214	18.9	384	307	20
Inactive rheumatic	279	291	0	450	454	0

Comparison of the mean areas of cutaneous dye diffusion with and without hyaluronidase, as affected by Subenon, are tabulated in Table V. As with salicylate therapy, succinate administration had no inhibitory effect on the spread of dye with and without the spreading factor enzyme in the inactive convalescing rheumatic fever group. However, in the nonrheumatic group, a 20 and 18.9 respective significant percentage reduction of dye spread with and without hyaluronidase was observed as the result of oral succinate administration.

The method used to determine the statistical significance of the differences between the mean areas of cutaneous dye diffusion of the compared groups was the "t" test of probability.[32] In comparing the mean areas, the value of t was calculated as equal to the ratio of the standard difference to the standard error of differences. Included in the statistical analysis, Table VI, are only the values of the mean group differences that were found to be significant.

No local or general sensitivity reactions or exacerbations of rheumatic activity occurred in the inactive rheumatic patients as the result of the repeated injections of the small amounts of the hyaluronidase enzyme. However, it has been reported[33] that a recurrence of activity with migratory polyarthritis

TABLE VI. STATISTICAL ANALYSIS OF MEAN DIFFERENCES BETWEEN VARIOUS MEAN DYE DIFFUSION AREAS

COMPARISON STATES		STANDARD DIFFERENCE $\bar{X}$	STANDARD ERROR OF DIFFERENCES $s\bar{X}$	t	P†	STATISTICALLY SIGNIFICANT
Nonrheumatic dye	Nonrheumatic dye with enzyme*	120	27.5	4.36	<0.01	Yes
Inactive rheumatic dye	Inactive rheumatic dye with enzyme	171	36.4	4.69	<0.01	Yes
Nonrheumatic dye with enzyme	Inactive rheumatic dye with enzyme	66	29.8	2.22	0.03	Yes
Nonrheumatic dye	Nonrheumatic dye with salicylate	47	22.9	2.05	0.04	Yes
Nonrheumatic dye with enzyme	Nonrheumatic dye with enzyme with salicylate	117	31.2	3.75	<0.01	Yes
Nonrheumatic dye	Nonrheumatic dye with succinate	50	18.3	2.73	<0.01	Yes
Nonrheumatic dye with enzyme	Nonrheumatic dye with enzyme with succinate	77	30.0	2.57	0.01	Yes

*Enzyme = hyaluronidase.

†P = statistical probability. As the criterion of significance, P denotes the probability that the different groups belong to the same population. Values of $P < 0.05$ are considered to denote a statistically significant difference between the groups.

occurred in a convalescing rheumatic fever patient after receiving four daily doses of 250 viscosity units of hyaluronidase, the amount generally used for normal hypodermoclysis fluid administration.

A comparison of male to female members in the twenty-two nonrheumatic subjects revealed no significant difference of their mean areas of dye diffusion with and without the enzyme hyaluronidase.

COMMENT

Of the many comparisons of the dye diffusion studies, most interesting is that the spreading effect of the dye with hyaluronidase was 17.1 per cent greater in convalescing inactive rheumatic patients as compared to nonrheumatic subjects. This result would tend to suggest that the cutaneous tissues of rheumatic patients possess a slightly increased allergy or susceptibility to the hyaluronidase enzyme. On basis of increased allergy to hyaluronidase, it may be the possible explanation why some patients develop rheumatic fever from a streptococcal infection and why other patients when exposed to the same infection merely have a streptococcal sore throat.

Also of interest is that the oral administration of sodium salicylate in nonrheumatic subjects resulted in a 30.4 and 17.8 per cent decrease of dye spread with and without the hyaluronidase enzyme, respectively. In the inactive rheumatic patients, salicylates exhibited no inhibition of cutaneous spread of the dye with or without the enzyme. Why the salicylates effected no decrease of dye spread in only the rheumatic patients is of special interest. Perhaps the rheumatic patients when tested had a resistance to the salicylate drug, or perhaps the supposed susceptibility to hyaluronidase in rheumatic patients is also concomitant with a property to develop hyaluronidase inhibitors. Also, perhaps the disturbed equilibrium between hyaluronic acid and hyaluronidase-antihyaluronidase in the mesenchymal tissue existing in rheumatic disease increases the threshold concentration for salicylates that can affect the connective tissue and produce a significant change manifested by the cutaneous dye diffusion method.

From these results it is most difficult to implicate salicylates as a specific antirheumatic agent, but it can be said that in nonrheumatic subjects salicylates do affect the hyaluronic acid substrate and hyaluronidase enzyme system which controls to a great extent the cutaneous diffusion of fluid made visible by use of dye alone. Also, as in nonrheumatic patients salicylates greatly decreased the spread of the hyaluronidase and dye mixture, it can be concluded that in these nonrheumatic patients salicylate drugs exhibited definite antihyaluronidase enzyme properties. The mode of inhibiting action of salicylates on the dye diffusion is not fully understood, but probably involves the combination of increased vascular hydration and some effect on the state of the interstitial ground substances as hyaluronic acid gel and others, and their mucolytic enzymes, one of which is hyaluronidase.

In discussing any of the above theorizations or attempting to suggest future directions and methods of investigation in this particular field, the

inherent disadvantages in the cutaneous dye diffusion method of study must be considered. Even though certain area differences are calculated to be significant, the especially high coefficients of variation of each mean make the dye diffusion method of measuring spreading factor activity far from ideal. The cutaneous diffusion of fluid is also a most complex biological process with many factors involved, therefore making specific deductions difficult to be interpreted. Pressure differences in the tissue from injection of the fluids themselves cause differences in spread. Also difficulties in uniform accurate standardization and purity of the hyaluronidase enzyme unfortunately tend to create slight variations of results of similar studies among hyaluronidase investigators.

Lastly, it is perhaps proper to mention briefly other present-day therapeutic advances which seem to further correlate hyaluronidase and hyaluronic acid to rheumatic fever. Recently there have appeared reports of dramatic amelioration of rheumatic fever and other mesenchymal diseases by the use of cortisone[34] and ACTH.[35] It was noted by Dwan and collaborators[36] that following ACTH therapy for a case of rheumatic fever, there was a distinct drop in the blood hyaluronidase inhibitor level. By studying diffusion in synovial membrane tissue of rabbits, Seifter and associates[37, 38] observed that hyaluronidase greatly increased the permeability of the synovial membrane and that cortisone and ACTH readily inhibited the increased permeability due to the hyaluronidase. The effect of cortisone and ACTH on cutaneous dye diffusion with the enzyme hyaluronidase in rheumatic states is presently being evaluated by Hench and associates[39] and Myers and Fischel,[40] the results of which should aid in the further correlation of hyaluronidase to the mesenchymal diseases.

SUMMARY

Cutaneous dye diffusion studies with and without hyaluronidase of bovine origin were performed on nonrheumatic and convalescing inactive rheumatic fever patients.

The mean area of dye diffusion with hyaluronidase was significantly greater in the inactive rheumatic group as compared to a control nonrheumatic group. These results suggest that the cutaneous tissues of rheumatic patients possess a slightly increased allergy or susceptibility to the hyaluronidase enzyme.

Oral administration of sodium salicylate and Subenon, a succinate compound, had no inhibitory effect on the spread of the dye with and without hyaluronidase in the inactive rheumatic fever patients.

However, in the nonrheumatic subjects, the oral salicylate and succinate therapy effected significant decreases of the cutaneous spread of the indicator dye with and without the enzyme hyaluronidase. Therefore, it can be said that in the nonrheumatic patients the salicylate and succinate drugs affected and altered the state of the hyaluronic acid and hyaluronidase enzyme system and also demonstrated antihyaluronidase enzyme properties.

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POSTVACCINAL ENCEPHALITIS IN INFANCY

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ENCEPHALITIS concurrent with successful vaccination against smallpox "does not occur in infants vaccinated in the first year of life" (Davison, 1946), "is practically unknown as a complication when vaccination is performed within the first year of life" (McNair Scott, 1950); "infants are almost immune" (Ford, 1945).[1-3]

These opinions are apparently derived from the English and Dutch studies of the relatively large number of cases of postvaccinal encephalitis studied about twenty years ago. Prior to October, 1929, apparently 177 cases occurred in England and Wales;[4-5] of these, eight were in infants under one year of age. All died; one was studied post mortem. The Dutch series of 124 cases, reported in 1927,[6] included one infant under 1 year of age. There are a few reports of other cases in infants, including that of Reisman and Utz, 1943.[7]

Not including the two infants described below, it is apparent that this complication of vaccination does occur in infants, and that the mortality is impressively high. The diagnosis has been made four times at the St. Louis Children's Hospital, and once at the St. Louis City Hospitals; of these five children, two were infants, and one died. The cases are described below. The three older children were 2½, 5½, and 12 years of age; all survived (Cases Z-2468, L-2090 at Children's, 72184 at City).

CASE REPORTS

Case 1.—L. R. (X-1026), a normal 5-month-old white female infant, who had never been ill or injured in any way, was vaccinated May 5, 1947. Twelve days later, the local reaction subsiding, she became listless and fretful. The following day she vomited some of her feedings. Examination at home, May 19, showed her to be obtunded, oblivious of her surroundings; the fontanel was tense; deep deflexes, hyperactive; back and neck, supple. No fever occurred at any time. At the hospital the spinal fluid was clear, with 2 lymphocytes per cubic millimeter; Ross-Jones test for protein negative; glucose levels in spinal fluid and blood normal. Study included routine blood counts and cultures, Kahn and tuberculin tests, urinalysis, and fluoroscopy of chest and long bones; all results were normal. In addition to cultures on the usual media, the blood and spinal fluid were cultured on the chorioallantoic membrane of the developing chick embryo and the rabbit cornea (through the cooperation of Dr. Russell Blattner and Dr. Florence Heys of the virus laboratory); no growth occurred.

The baby was unable to take feedings. Painful stimuli produced no response. She quietly expired May 21, without convulsions or other dramatic phenomena. Lumbar puncture on May 20 showed 10 lymphocytes; on May 21, 45 lymphocytes per cubic millimeter; both fluids showed a positive Ross-Jones test for protein.

Autopsy, performed by Dr. P. R. Beamer, resulted in relatively meager findings: "Flattening of the cerebral convolutions, slight internal hydroceph-

alus, edema of the leptomeninges. The six sections from the brain are similar. There is a slight amount of edema fluid in the meninges. Otherwise the sections are not remarkable. Sections stained with osmic acid show no pathologic change.'' Post-mortem cultures of spinal fluid, blood, and cerebral tissue showed no growth on blood agar, nutrient broth, or the chorioallantoic membrane of the developing chick embryo.

CASE 2.—J. A. M. (W-2051), 7 months of age, was apparently normal until twelve days after successful smallpox vaccination. When irritability, fever, and a stiff neck were noted, the baby was referred to Dr. Russell Blattner and admitted to the Children's Hospital. The first spinal puncture resulted in gross blood; repeated Oct. 26, 1946, the fluid contained 86 leucocytes per cubic millimeter, 72 per cent polymorphonuclears; Ross-Jones test was positive. The next day the fluid contained 72 leucocytes, 50 per cent polymorphonuclears. No new symptoms developed; the irritability decreased, and the baby was discharged in good condition three days after admission. The laboratory studies were identical with those performed in the case of infant L. R., and all results were normal.

It seems apparent that postvaccination encephalitis in infancy may not be as rare as has seemed true. Since two of our five cases occurred in infants, one is led to believe that other cases in this age group will be reported.

SUMMARY

Two cases of postvaccination encephalitis in infancy, occurring at 5½ and 7 months of age, are reported. The younger baby died.

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FEEDING OF PREMATURE INFANTS

Use of a Simple Formula

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In 1948 Adams[1] reported a series of fifty-six cases of premature infants fed a simplified formula consisting of half evaporated milk and half water without added carbohydrate. This constituted a high fat and low carbohydrate mixture with 52 per cent of the calories supplied by fat, 28 per cent supplied by carbohydrate, and 20 per cent supplied by protein. His results compared favorably with the results obtained by Hess[2] in babies fed in a more orthodox manner. This led the Journal of Pediatrics to comment editorially[3] that independent confirmation of these results was necessary before the practitioner should turn from accepted methods to the simpler method proposed.

The purpose of this paper is to report my results and experiences with the use of this simple type of feeding in a much larger series at the same hospital during 1948 and 1949 after Dr. Adams' return to civilian life.

All babies were born at the U. S. Naval Hospital at San Diego, Calif. Most of the infants were delivered by interns and residents in training. The medical care of all the premature infants, however, was supervised by me. Changes in nursing personnel were frequent but these were kept at a minimum so far as was possible. The premature nursery census averaged about six babies at a time with variations of from two to ten. One nurse was on duty at all times. Gordon Armstrong incubators and heated cribs were used.

The method of feeding the simple formula, half evaporated milk and half water, which was terminally sterilized, was essentially the same as used by Adams except that a longer period of withholding water or formula was adopted because of the recommendations and findings of Clifford[4] and Smith.[5] They showed that premature infants, especially the smaller ones, were frequently edematous, either as the expression of a natural mechanism or the result of anoxia. These authors felt that a "drying out" period of thirty-six to seventy-two hours was beneficial and physiologic, in that excess fluid was lost with consequent relief of cerebral and pulmonary edema as well as generalized water logging. In addition, withholding feedings avoided the danger of aspiration. In our babies during the first twelve hours of feeding, calculated amounts of glucose water were given every three hours; during the next twenty-four hours the glucose water was alternated with the half-and-half formula, and finally formula feedings alone were given. Eight cubic centimeters was the base amount

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as recommended by Gordon[6] for a 1,500 gram (3 pounds, 5 ounces) infant, and the amount was lowered or increased proportionately in the case of smaller or larger infants. For example, a 1,100 or 1,200 gram infant was started on 4 c.c., while a 1,800 gram baby initially could safely be given 15 c.c. All infants under 2,000 grams (4 pounds, 6 ounces) were gavaged using 10 or 12 French catheters. The three-hour interval was used in the case of babies over 3 pounds (1,360 grams) and the two-hour interval in those under that weight; however, the latter was not begun until the baby was 6 or 7 days old, when the need for fluid and food became greater. Increases of the initial amounts were made gradually after consultation with the attending nurse. The quantity given was determined primarily by the infant's ability to take his feedings without undue abdominal distention, respiratory difficulty, cyanosis, or regurgitation. In general, the babies were gavaged the maximum amount of the formula they could safely ingest. Under this regime of gavage of gradually increasing amounts, vomiting was infrequent, and pulmonary complications not conditioned by intrauterine factors or those incident to the delivery were rare. Usually 150 to 200 c.c. per kilogram per day were tolerated some time during the second week and this amount was adequate to satisfy the caloric requirements of 110 to 140 calories per kilogram as well as the infants' fluid needs. Only when we felt that satisfactory progress was not being made, did we work back to check if the caloric and fluid intake was sufficient. Subcutaneous clyses of 5 per cent glucose were occasionally necessary. This was usually at the beginning of the second week when apathy and other signs of dehydration were often evident. Intravenous fluids or intravenous plasma or blood were given only to those requiring abdominal surgery. Oxygen and antibiotics were administered freely. Water-soluble multivitamins preparations (Vi-Penta, Vi-Syneral, or Poly Vi Sol) in dosage of 10 drops twice a day were started the day after oral feedings were begun. No vitamin E was given. Intramuscular crude liver extract, ½ c.c., was administered twice weekly after the fifth day as recommended by Powers.[7] Ferrous sulfate elixir (Feosol) was begun at the age of one month. Although several smaller infants developed red counts of about 2.5 million, transfusions were felt to be unnecessary as the infants were thriving and comfortable in spite of the anemia and their later development after leaving the hospital was uneventful.

Stools varied from one to six daily and were pasty and nonirritating. Sore buttocks and occasional loose stools were evanescent and of no consequence. On no occasion was the formula changed. When a temporary disturbance suggested that less food should be given, glucose water was fed instead of milk.

RESULTS AND COMMENTS

Incidence and Fatality Rates.—During the two-year period there were 4,271 live births and of these 311 weighed less than 2,500 grams (5 pounds, 8 ounces), making an incidence of prematurity of 7.28 per cent. Our total incidence and percentage of various weight groups are compared (Table I) with the recent study made jointly under the auspices of the American Academy of Pediatrics

TABLE I. INCIDENCE OF PREMATURITY

WEIGHT GROUPS (GRAMS)	NO.	% TOTAL BIRTHS	% TOTAL PREMATURE INFANTS	BAIN ET AL.[8] % TOTAL PREMATURE INFANTS
Under 1,000	19	0.44	6.1	6.8
1,001-1,500	33	0.77	10.6	9.9
1,501-2,000	60	1.40	19.3	20.2
2,001-2,500	199	4.67	64.0	63.1
	311	7.28		

Bain, Hubbard, and Pennell: Based on reports from 193 hospitals.

Total births	308,487
Number of premature infants	18,895
Incidence of prematurity	6.1%

and Federal Security Agencies by Bain and collaborators,[8] comprising the reports of 193 hospitals with over 300,000 births.

Among our 311 cases there were fifty-three deaths, a fatality rate of 17 per cent. This number included all babies having any evidence of life, viable or nonviable, but who were not obviously stillborn. Our rate compares favorably with the results of the Academy sponsored study of 23.7 per cent based on over 25,000 premature babies born in 277 hospitals (Table II) and fatality rates from various sources as shown in Table III. Only seven babies (13 per cent) died after the age of 4 days and all but one presented at autopsy definite pathological conditions where the type of feeding could not have contributed to the death (Table IV). Eighty-seven per cent died before the age of 4 days and of course before much of any food was given. This compares with 86.5 per cent within the first week (U. S. Bureau of Census for 1944),[7] and 89.5 per cent within the first 4 days (Beth-El Hospital, Brooklyn),[9] and 93 per cent

TABLE II. MORTALITY RATE BY WEIGHT GROUPS

	U. S. NAVAL HOSPITAL SAN DIEGO, CALIF.			*REPORTS FROM 277 HOSPITALS
WEIGHT GROUPS (GRAMS)	NO.	DEATHS	RATE %	RATE %
Under 1,000	19	19	100.0	89.6
1,001-1,500	33	21	63.6	54.4
1,501-2,000	60	5	8.3	22.8
2,001-2,500	199	8	4.0	7.3
	311	53	17.0	23.7

*Bain and collaborators[8]: Study based on 25,594 premature infants, with 6,096 deaths.

TABLE III. MORTALITY RATES FROM VARIOUS HOSPITALS

INSTITUTION OR AUTHOR	NO.	RATE %
U. S. Naval Hospital, San Diego	311	17
Bain et al.[8]	32,000	21.5
Chicago Lying-in[8]		18.2
Boston Lying-in[10]		16
Beth-El, Brooklyn[9]	992	13.5
Hess[2]		27.5
Stoesser[2]		26.8
Grace-New Haven Hospital[7]	800	22
Infants born outside and later admitted to hospital[8]	2,000	36.6

TABLE IV. DATA ON SEVEN BABIES DYING AFTER AGE OF 4 DAYS

BIRTH WEIGHT	AGE AT DEATH (DAYS)	AUTOPSY FINDINGS
4 lb., 5 oz.	30	Intestinal obstruction due to Meckel's diverticulum
2 lb., 2 oz.	9	No findings other than prematurity
1 lb., 15 oz.	13	Sepsis
4 lb., 10 oz.	11	Congenital heart malformation
2 lb., 6 oz.	21	Intestinal obstruction due to myenteric agenesis
4 lb., 6 oz.	16	Intracranial hemorrhage
2 lb., 14 oz.	9	Bronchopneumonia

within the first week (Boston Lying-in Hospital).[10] In this connection, Powers'[7] view is noteworthy, that mortality rates are only one measure of evaluating premature care and feeding, and qualitative differences in food are not likely to be reflected in the mortality rates. We agree and feel that mortality rates are influenced to a greater extent by obstetrical difficulties and maternal disease. This was pointed out recently by Taylor and collaborators[11] in a study of 446 premature infants where the neonatal mortality was 26 per cent in complicated pregnancies and only 5 per cent in the uncomplicated ones.

Table V presents the average day on which the birth weight was regained. Our figures of 14.6, 13.2, and 11.2 days for babies weighing 1,000 to 1,500, 1,500 to 2,000, and 2,000 to 2,268 grams, respectively, are compared with the figures of others. The short time necessary to regain the birth weight in Gruber's large group from the Beth-El Hospital in Brooklyn[9] is noteworthy and would indicate that one-third evaporated milk diluted with two-thirds water plus 5 per cent dextrimaltose was superior to other formulas or breast milk in facilitating rapid regaining of birth weight.

TABLE V. AVERAGE NUMBER OF DAYS NECESSARY TO REGAIN BIRTH WEIGHT

BIRTH WEIGHT	PRESENT STUDY	ADAMS[1]	GRUBER ET AL.[9]	HESS[2]	BRUCE ET AL.[13]
1,001-1,500	14.6	13.9	9.9	18.6	
1,501-2,000	13.2	12.8	8.3	14.4	
2,001-2,268	11.1				
2,001-2,500	*	10.8	5.1	11.8	
1,000-2,500					18.7†

So many of the larger babies left hospital before birth weight was regained; reliable figures were unobtainable.

†Average figure for four groups fed different mixtures, varying from 14.7 days for Similac to 21.6 days for breast milk plus skimmed lactic acid milk.

Table VI presents the average length of stay in the hospital. Our figures for the 1,000 to 2,000 gram group are much the same as the results of others. It has been our policy to discharge babies at about 5 pounds (2,268 grams). However, other considerations, such as the physical condition of the individual baby, the season of the year, home conditions, and finally the limitations of nursery space and nursing personnel, help to determine the time of discharge. These facts probably account for our relatively low figure of 10.8 days in the case of the group of larger infants.

TABLE VI. AVERAGE LENGTH OF STAY IN HOSPITAL IN DAYS

BIRTH WEIGHT	PRESENT STUDY	ADAMS	GRUBER ET AL.	HESS
1,000-1,500	51.2	45.3	50.7	45.7
1,501-2,000	29.2	30.7	32.2	30.5
2,001-2,500	10.8	17.7	11.5	19.9

Table VII presents the mean weight gain in grams per kilogram per day between the seventh and the twenty-eighth day. This method was suggested by Gordon and co-workers[12] as a means of evaluating a type of feeding formula. Here again our results compare favorably with the figures of others using various types of milk mixtures as well as breast milk. Especially noteworthy is that fact that the smallest premature infants, as well as the larger babies, gained well on the formula.

TABLE VII. MEAN WEIGHT GAIN IN GRAMS PER KILOGRAM PER DAY SEVENTH TO TWENTY-EIGHTH DAY

	ABELSON EVAP. MILK NO D.M.*		GRUBER[9] EVAP. MILK 5% D.M.		GORDON[12] EVAP. MILK 5% D.M.		GORDON[12] HALF SKIMMED MILK & D.M.		GORDON[12] HUMAN MILK	
BIRTH WT.	GRAMS	CASES	GRAMS	CASES	GRAMS	CASES	GRAMS	CASES	GRAMS	CASES
1,001-1,500	18.7	12	15.3	28	14.9	14	17.3	31	11.7	4
1,501-2,000	12.7	33	12.7	149	13.7	25	14.2	36	12.7	12

*Dextrimaltose.

ACIDOSIS

Spontaneous acidosis with hyperpnea and apathy occurred in eight cases. None of these infants had vomiting, diarrhea, or any precipitating factor. Treatment with 10 to 15 gr. of sodium bicarbonate daily divided in the feedings or/and the parenteral administration of Ringer's lactate solution resulted in marked clinical improvement in thirty-six to forty-eight hours. There were no deaths from this complication. Carbon dioxide combining power determinations were done on the first few cases with results of 15, 18, and 20. No other serum electrolyte studies were done as we became clinically adept in the recognition and treatment of this syndrome and facilities for reliable determinations were unavailable.

That spontaneous acidosis is not uncommon in premature infants under various types of feeding was early pointed out by McBryde and Branning.[14] Studies by Darrow and collaborators,[15] and recently confirmed by Hoffman and his co-workers,[16] emphasized its regular occurrence in premature infants fed protein milk. Darrow was able to prevent its occurrence by the addition of sodium bicarbonate to the milk powder. Hoffman and collaborators[17] in an additional study of premature infants fed evaporated milk mixtures with added carbohydrate showed increased concentration of serum chloride and lowered bicarbonate concentrations without clinical manifestations of hyperpnea or apathy. Apparently our cases were more severe than those encountered by Hoffman and co-workers and would suggest that the addition of carbohydrate in the formula protected the infants from clinically manifest acidosis, although

in Darrow's studies the addition of carbohydrate to protein milk lessened this acidotic tendency only slightly. Hoffman and collaborators observed that, slowly with increased efficiency in renal function, the chloride concentration was reduced to levels near to that found in adults. They felt that evaporated milk mixtures with added carbohydrate were nutritionally a satisfactory diet for premature infants but interposed, because of their findings, theoretic objections to the limited dilution of evaporated milk which, though establishing a high protein intake, forces at the same time a high chloride and potassium intake. Ideally they contended the milk should be diluted to reduce the mineral content of the diet and a form of extra protein should be added which does not contain minerals. Darrow's suggestion of the addition of 2 c.c. of a 6 per cent solution of sodium citrate to each 100 c.c. of formula mixture is used by Powers[7] to counteract the excess chloride in undiluted milk. From a clinical point of view, the occasional case of manifest acidosis has never been a serious complication, but nevertheless offers the only objection to the use of the simplified formula. In the past few months after studying the problem of acidosis in conjunction with this report, we have added the sodium citrate solution to our formulas. No cases of acidosis have been encountered during this period, but, of course, the time has been too short for us to determine its efficacy clinically.

RETROLENTAL FIBROPLASIA

Recently, Owens and Owens[18] advocated the use of vitamin E for the prevention of retrolental fibroplasia. They point out that a low fat diet is usually recommended for premature babies because of their defective fat metabolism. These authors cite this low fat diet as being a factor in allowing premature infants to have only marginal amounts of vitamin E available since it contains very little of the fat soluble vitamins. In our series no vitamin E was given, yet no case of retrolental fibroplasia occurred. Although the number of babies susceptible to retrolental fibroplasia in this study is small, it is suggested that the high fat diet was possibly a factor in the prevention of this dreaded eye complication.

SUMMARY AND CONCLUSIONS

1. A series of 311 premature babies fed on a simple formula of half evaporated milk and half water is studied.

2. Mortality rates, days necessary to regain birth weights, average length of stay in hospital, and mean weight gain in grams per kilogram from the seventh to the twenty-eighth day are found to compare favorably with the reports of others using more standard feeding formulas or/and breast milk.

3. It is suggested the high fat content of the half-and-half mixture may have helped to prevent the occurrence of retrolental fibroplasia.

4. It is concluded that the simple formula of half evaporated milk and half water without added carbohydrate is a suitable food for the feeding of premature infants.

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SENSITIVITY OF DIPHTHERIA BACILLI AND RELATED ORGANISMS TO NINE ANTIBIOTICS

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THE discovery and development of several new antibiotics with a wide range of efficacy have made possible the successful treatment of a large variety of microbial infections. As a result, many infectious diseases are now benefited by each of several antibiotics so that a choice of agents is available for the treatment of such diseases. In making the selection of an agent for use in any given disease, one of the primary considerations is the relative sensitivity of the offending microorganism. The present report deals with the results of in vitro tests for sensitivity of virulent strains of *Corynebacterium diphtheriae* and of some related organisms performed simultaneously with nine antibiotics. This was undertaken as part of a broader study of the sensitivity of the common species of human pathogenic bacteria to the more important antibiotics that have become available.

MATERIALS AND METHODS

Isolation and Identification of Strains.—After primary culture on slants of Loeffler's medium, the strains were isolated in pure culture on blood agar by Miss Marion E. Lamb of the Bacteriological Laboratory of the Mallory Institute of Pathology. The strains were classified by their colonial morphology after growth for forty-eight hours on Mueller-Miller tellurite medium and by their fermentation reactions with starch, dextrose, and sucrose in Hiss serum water. A virulence test was done for each strain using the guinea pig intracutaneous method.

Strains of *C. diphtheriae* were classified as follows: *Mitis*—grew as small, moist, shiny, dome-shaped, black colonies on tellurite medium; they fermented dextrose with acid formation but did not ferment starch or sucrose. *Gravis*—formed large, flat, dark gray, opaque colonies on tellurite medium; they fermented both starch and dextrose but not sucrose. *Intermedius*—formed tiny, flat, gray, opaque colonies; they fermented dextrose but not starch or sucrose. The strain classified as *C. xerose* produced acid from dextrose and sucrose but not from starch; those classified as *C. pseudodiphtheriticum* failed to produce acid from any of these carbohydrates. Other strains that could not be classified by the methods used were listed as "diphtheroids."

Sources of the Strains Tested.—A total of forty-nine strains were included in this study, as follows:

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) and the South Department, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

Aided by a grant from the United States Public Health Service.

C. diphtheriae, type *mitis*—Thirty-one virulent and five avirulent strains. The Park strain, obtained from Dr. R. A. MacCready of the Diagnostic Laboratory, Massachusetts Department of Health, was included among the former; all the rest were recently isolated from patients and carriers at the South Department of the Boston City Hospital. Two of the virulent strains were obtained from cutaneous ulcers, two others from sputum and the remaining *mitis* strains were isolated from nose and throat cultures. Four of the avirulent strains were from convalescent carriers who had previously received penicillin therapy, the fifth was from a chronic carrier.

C. diphtheriae, type *gravis*—Two strains. One of them, No. 12, was obtained from Dr. J. H. Mueller of the Harvard Medical School and the other, No. 13, from Dr. M. Frobisher, Jr., of the Communicable Disease Center, Chamblee, Ga.

C. diphtheriae, type *intermedius*—Three strains. One of these was isolated from the pharynx of an acute case at the South Department and the other two, Nos. 15 and 16, were obtained from Dr. Frobisher.*

C. pseudodiphtheriticum—Four strains. One of these was obtained from a blood culture and the other three from routine throat cultures.

C. xerose—One strain from a routine throat culture.

"Diphtheroids"—Three strains. Two were isolated from routine blood cultures and presumably were contaminants and the third was obtained from conjunctival exudate.

Antibiotics.—The following antibiotics were used:

Crystalline penicillin G, potassium salt (Commercial Solvents Corporation) 1,595 units per milligram.

Bacitracin, 40 units per milligram.†

Streptomycin (calcium chloride complex) (Merck).

Neomycin sulfate, 173 units per milligram.†

Crystalline aureomycin hydrochloride.‡

Chloroamphenicol (Chloromycetin).§

Terramycin hydrochloride.‖

Polymyxin B (Aerosporin).‖

Polymyxin (Polymyxin D, Lederle, B 71).‡

The concentrations of these antibiotics were all prepared on a weight basis (in micrograms per milliliter).

Tests for Sensitivity.—The method was essentially the same as that used for other organisms. A series of plates was prepared with beef heart infusion agar (Difco), pH ± 7.2, containing 10 per cent horse blood and twofold dilutions of the various antibiotics in the appropriate range. The plates were marked in sections and each section was streaked with a 1 ml. loopful of a fully grown,

*Strain No. 13 was classified by Dr. Frobisher as "*intermedius*" and strains 15 and 16 as "*minimus*."

†Supplied by Dr. Lawrence W. Smith of Commercial Solvents Corporation.

‡Furnished by Dr. Stanton M. Hardy of Lederle Laboratories.

§Provided by Dr. E. A. Sharp of Parke, Davis & Co.

‖Obtained from Dr. Gladys L. Hobby of Chas. Pfizer & Co., Inc.

blood-broth culture of one of the strains. Ten to twenty strains were tested simultaneously with all of the antibiotics. Because some antibiotics, notably aureomycin, deteriorate rapidly in neutral or alkaline solution, the plates were streaked promptly after they solidified. The surface of the plates was examined for growth under a good light and with an engraver's lens (3x) after twenty-four hours and again after forty-eight hours of incubation at 37° C. The minimum concentration of antibiotic on which there was no discernible growth after forty-eight hours was considered the "sensitivity" or "complete inhibiting concentration"; the endpoint for "partial inhibition" was taken as the minimum concentration on which either numerous minute colonies or only a few larger colonies were observed after twenty-four hours. Streptococcus 98 and *Klebsiella pneumoniae*, strain T, were included as control cultures in each test; the sensitivity of these strains showed no more than a twofold variation in the different tests.

RESULTS

The concentrations of each of the antibiotics required for partial and complete inhibition of twenty-four of the strains tested are shown in Table I. Included are the Park strain, five additional strains which are representative of the recently isolated, virulent *mitis* strains, and all of the other strains that were tested. A few pertinent features of these data may be pointed out.

In the first place it is seen that the virulent and the avirulent *mitis* strains as well as the other types of *C. diphtheriae* and the related organisms (with the exception of *C. xerose*) were, in a very general way, similar in their sensitivity to each of the antibiotics. However, except for the virulent *mitis* strains, there were not available a sufficient number of specimens of each type to make any detailed or statistically valid comparisons. It may also be seen that, in general, penicillin and bacitracin were the most active agents against all of the strains and these two agents had quite similar activity, on a weight basis against each strain. Aerosporin and polymyxin D were the least active; all of the strains tested grew profusely in 200 μg per milliliter of the latter. The remaining antibiotics were active in an intermediate range.

Finally, it is seen that there was considerable variation in the "range of partial inhibition" (that is, in the ratio of complete to partial inhibiting concentrations) among the different antibiotics and, to a lesser extent, among the individual strains, when tested with the same agent. The sharpest endpoints of inhibition were observed with bacitracin; none of the strains showed more than a twofold difference between the partial and complete inhibiting concentrations of this antibiotic. Aerosporin, chloromycetin, and penicillin ranked next in this respect; the majority of the strains showed only a twofold or fourfold spread between partial and complete inhibiting concentrations of these agents although some individual strains showed a wider range of partial inhibition with these agents. With the remaining antibiotics—aureomycin, Terramycin, streptomycin, and neomycin—only a few strains were inhibited by concentrations twofold to fourfold greater than the minimum concentration required for partial inhibition, while many showed an eightfold or greater range of partial inhibition.

TABLE I. SENSITIVITY OF TWENTY-FOUR STRAINS OF CORYNEBACTERIA TO EIGHT ANTIBIOTICS*

NO.	STRAIN†	SOURCE	MINIMUM INHIBITING CONCENTRATIONS, MICROGRAMS PER MILLILITER															
			PENICILLIN		BACITRACIN		AUREOMYCIN		CHLOROMYCETIN		TERRAMYCIN		STREPTOMYCIN		NEOMYCIN		AEROSPORIN	
			P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C
1	M	W.H.P.	0.05	0.1	0.1	0.2	0.4	12.5	3.1	6.3	0.4	12.5	3.1	50	0.4	3.1	25	50
2	M	Pharynx	0.1	0.2	0.4	0.4	0.4	3.1	0.8	0.8	0.8	1.6	1.6	3.1	0.4	3.1	100	200
3	M	Pharynx	0.1	1.6	0.1	0.2	0.8	6.3	0.8	3.1	0.4	0.8	0.8	6.3	0.8	1.6	100	200
4	M	Sputum	0.1	1.6	0.1	0.1	0.8	6.3	0.8	3.1	0.8	1.6	1.6	25	0.8	1.6	50	100
5	M	Ulcer	0.2	0.4	0.2	0.2	0.8	3.1	1.6	3.1	0.4	1.6	1.6	6.3	0.8	3.1	100	200
6	M	Ulcer	0.1	0.4	0.1	0.2	0.8	6.3	0.8	1.6	0.4	1.6	1.6	6.3	0.4	1.6	100	100
7	M-A	Pharynx	0.1	0.8	0.2	0.2	0.8	12.5	1.6	1.6	0.8	6.3	3.1	12.5	0.8	0.8	50	100
8	M-A	Pharynx	0.1	0.8	0.05	0.1	1.6	12.5	0.8	6.3	0.4	3.1	1.6	12.5	0.8	12.5	50	200
9	M-A	Pharynx	0.05	0.4	0.1	0.2	0.8	12.5	0.8	3.1	0.4	3.1	1.6	12.5	0.4	0.8	<25	25
10	M-A	Pharynx	0.2	0.4	0.05	0.1	0.4	12.5	1.6	3.1	0.8	3.1	3.1	12.5	0.5	2.0	100	200
11	M-A	Pharynx	0.2	0.4	0.1	0.2	0.4	3.1	1.6	1.6	0.4	3.1	3.1	25	0.5	2.0	100	200
12	G	H.M.S.	0.1	0.8	0.05	0.1	0.8	6.3	0.8	1.6	0.4	0.8	1.6	12.5	0.8	6.3	50	50
13	G	C.D.C.	0.05	1.6	0.1	0.2	1.6	12.5	1.6	6.3	0.4	1.6	0.8	3.1	0.4	1.6	25	200
14	I	Pharynx	0.1	0.2	0.4	0.4	0.2	1.6	0.8	1.6	0.4	0.8	1.6	3.1	0.4	1.6	100	200
15	I	C.D.C.	0.1	0.2	0.2	0.2	1.6	12.5	1.6	6.3	0.8	3.1	3.1	6.3	1.6	12.5	100	200
16	I	C.D.C.	0.1	0.1	0.2	0.2	1.6	12.5	1.6	3.1	0.4	6.3	3.1	6.3	1.6	12.5	50	200
17	P	Pharynx	0.05	0.1	0.1	0.2	1.6	12.5	3.1	3.1	1.6	6.3	0.8	3.1	0.2	0.4	25	25
18	P	Pharynx	0.05	0.1	0.1	0.2	1.6	12.5	3.1	6.3	1.6	6.3	0.8	3.1	0.2	0.8	25	50
19	P	Blood	0.025	0.05	0.025	0.05	0.4	6.3	3.1	3.1	1.6	3.1	1.6	6.3	0.2	0.8	6.3	12.5
20	P	Pharynx	0.05	0.2	0.025	0.05	0.8	12.5	3.1	6.3	1.6	3.1	1.6	6.3	0.2	0.8	6.3	12.5
21	X	Pharynx	0.1	0.8	0.8	1.6	0.8	12.5	3.1	6.3	1.6	6.3	25	50	100	200	>400	>400
22	U	Blood	0.025	0.4	0.025	0.025	0.4	6.3	0.4	3.1	0.2	3.1	0.2	1.6	0.1	0.2	6.3	12.5
23	U	Blood	0.1	0.2	0.025	0.025	0.4	3.1	1.6	6.3	0.8	3.1	1.6	6.3	0.1	0.8	12.5	25
24	U	Eye	0.025	0.05	0.025	0.05	0.8	12.5	3.1	12.5	1.6	12.5	3.1	12.5	0.4	0.8	6.3	12.5
98	S.H.	Stock	0.01	0.01	0.2	0.4	0.4	6.3	3.1	6.3	0.8	12.5	25	25	—	—	100	200
T	F.B.A.	Stock	—	—	—	—	3.1	12.5	1.6	3.1	1.6	6.3	1.6	1.6	0.8	3.1	0.8	1.6

*Results with Polymyxin D are not listed since all strains tested grew profusely on 200 μg per milliliter, the highest concentration used.
†M = *Corynebacterium diphtheriae*, type *mitis*, virulent; M-A = *C. diphtheriae*, type *mitis*, avirulent; G = *C. diphtheriae*, type *gravis*; I = *C. diphtheriae*, type *intermedius* (G and I strains were all virulent); P = *C. pseudodiphtheriticum* (Hoffman's bacillus); X = *C. xerose*; U = other unclassified bacilli (diphtheroids). Strain 98 (S.H.) = *Streptococcus pyogenes*, Group A, type ?, obtained from Dr. C. S. Keefer; Strain T (F.B.A.) = *Klebsiella pneumoniae*, type A obtained from sputum.

Other abbreviations: P = partial; C = complete; W.H.P. = Park strain obtained from Dr. R. A. MacCready of the Diagnostic Laboratory, Massachusetts Department of Public Health; H.M.S. = Harvard Medical School (strain obtained from Dr. J. H. Mueller); C.D.C. = Communicable Disease Center, U.S.P.H.S., Chamblee, Ga. (strains obtained from Dr. M. Frobisher, Jr.).

More detailed comparisons of the antibiotics were possible with respect to their activity against the thirty-six virulent strains. A cumulative distribution curve of the "sensitivity" (that is, the complete inhibiting concentration) of these strains was constructed for each of the antibiotics. The curves for all nine of the antibiotics are shown together in Fig. 1 which may be considered as constituting an "antibiotic spectrum" for the virulent strains of diphtheria bacilli. From this figure one may more readily arrange the antibiotics in the order of their in vitro activity, on a weight basis, as follows: (1) bacitracin, (2) penicillin, (3) Terramycin, (4) Chloromycetin, (5) neomycin, (6) aureomycin, (7) streptomycin, (8) aerosporin, and (9) polymyxin. The range of concentrations of these antibiotics which are required to inhibit the great majority of these virulent strains are listed for convenience in Table II. So far as one may judge from the data shown in Table I, it seems likely that the antibiotic spectrum for all types of *C. diphtheriae*, and for most of the related species as well, would be essentially the same.

TABLE II. RANGE OF CONCENTRATIONS OF NINE ANTIBIOTICS WHICH COMPLETELY INHIBIT MORE THAN 80 PER CENT OF VIRULENT STRAINS OF C. DIPHTHERIAE

ANTIBIOTIC	MINIMUM COMPLETE INHIBITING CONCENTRATIONS, MICROGRAMS PER MILLILITER	PER CENT OF STRAINS
Bacitracin	0.2-0.4	89
Penicillin	0.2-0.8	86
Terramycin	0.8-3.1	92
Chloromycetin	1.6-6.3	92
Neomycin	1.6-6.3	83
Aureomycin	3.1-6.3	83
Streptomycin	3.1-6.3	83
Aerosporin	100-200	92
Polymyxin	>200	100

It is of interest to note that this is the only instance among the various aerobic, human pathogenic bacteria studied in this laboratory in which bacitracin appeared to be generally more active than penicillin. The difference in activity of these two agents, however, was only slight. The curves of the next five agents, although well removed from the first two, fell fairly close together indicating that they were all quite similar in their activity. Aerosporin and polymyxin were by far the least active as shown by the fact that the curves for these agents were far removed to the right of this figure.

A comparison of the range of partial inhibition of the virulent *mitis* strains by the various antibiotics is shown in Fig. 2. In this figure separate cumulative distribution curves of partial and of complete inhibiting concentrations are shown side by side for eight of the antibiotics. The relative ranges of partial inhibition by the different antibiotics that were indicated for the individual strains in Table I are shown here to be similar for the entire group of virulent strains. Thus, for bacitracin the sharp endpoints are reflected in this figure by both curves falling together, or nearly so, for most of their length. The pairs of curves for aerosporin and Chloromycetin are fairly close together and, in each instance, the curve representing partial inhibition is subtended by that for

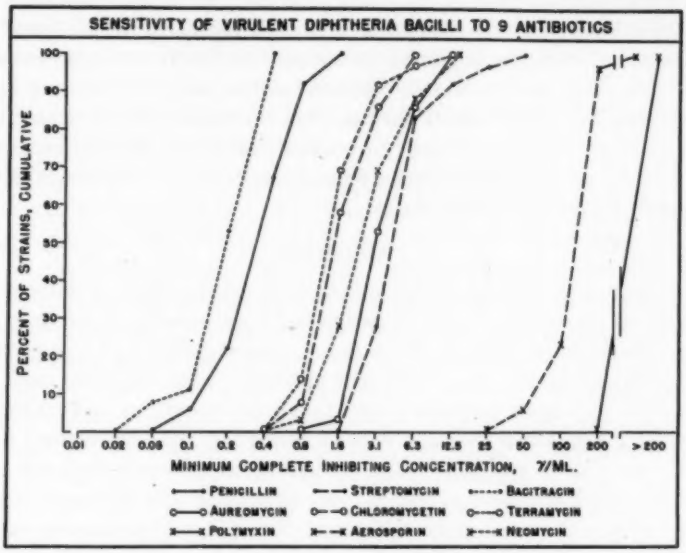
SENSITIVITY OF VIRULENT DIPHTHERIA BACILLI TO 9 ANTIBIOTICS
PERCENT OF STRAINS, CUMULATIVE
MINIMUM COMPLETE INHIBITING CONCENTRATION, γ/ML.
PENICILLIN
STREPTOMYCIN
BACITRACIN
AUREOMYCIN
CHLOROMYCETIN
TERRAMYCIN
POLYMYXIN
AEROSPORIN
NEOMYCIN

Fig. 1.

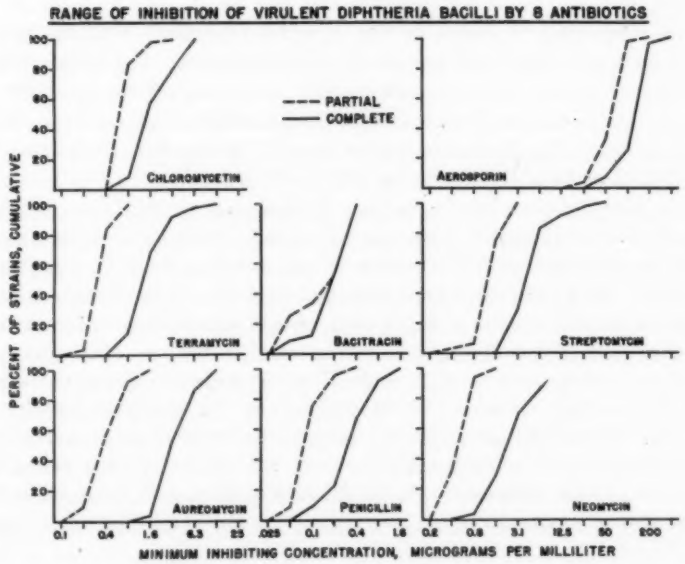
RANGE OF INHIBITION OF VIRULENT DIPHTHERIA BACILLI BY 8 ANTIBIOTICS
PARTIAL
COMPLETE
PERCENT OF STRAINS, CUMULATIVE
CHLOROMYCETIN
AEROSPORIN
TERRAMYCIN
BACITRACIN
STREPTOMYCIN
AUREOMYCIN
PENICILLIN
NEOMYCIN
MINIMUM INHIBITING CONCENTRATION, MICROGRAMS PER MILLILITER

Fig. 2.

complete inhibition for almost the entire length of the latter. The same is true, though to a less extent, for penicillin. On the other hand, only a small portion of the curves of complete inhibiting concentrations for Terramycin, aureomycin, streptomycin and neomycin falls directly under the corresponding curve of partial inhibition. This reflects the fact that the concentration of each of these four antibiotics which is sufficient to produce significant though incomplete inhibition of all of the strains was adequate to produce complete inhibition of only a small proportion of the strains.

DISCUSSION

The wide discrepancies in the values reported by different authors for the sensitivity of diphtheria bacilli to penicillin[1-5] and streptomycin[6] may be misleading. Marked variations in the values for the sensitivity of any given strain may be obtained by the use of different methods. Thus, with the methods now most widely used such variations were found to exceed one hundredfold.[7] In the present study, all of the tests were performed by the same method and with all of the antibiotics simultaneously. It is realized, however, that this does not necessarily yield completely reliable comparisons of the different antibiotics, since the effects of such factors as deterioration, pH, certain constituents of the medium, protein binding, and the size of the inoculum varies with the different agents. The method used in this study has been found to give generally high values, nevertheless it allows a useful, if not completely satisfactory, comparison of the in vitro activity of the different antibiotics.

This comparison is shown in Fig. 1, which represents what has been called an antibiotic spectrum for virulent diphtheria bacilli. The slope of the individual curves in this spectrum reflects the uniformity of the sensitivity of different strains as defined in this study. The horizontal span of each curve thus represents the range of concentrations required to produce complete inhibition of the growth of all of the strains for forty-eight hours.

The curves for streptomycin and Terramycin in this spectrum show an exaggerated bend near the upper end followed by a somewhat longer and flatter portion as compared with the curves of the other agents. This indicates that some of the strains require a significantly higher than average concentration for complete inhibition and suggests, in turn, that diphtheria bacilli are quite heterogeneous in their sensitivity to these two agents. In the case of streptomycin this may, in some instances, be the result of the emergence of isolated colonies of relatively resistant variants. With Terramycin, on the other hand, the wide span of the curve is apparently the result of differences in strain sensitivity since uniformly increased suppression of growth was observed with increasing concentrations of this antibiotic. As shown in Fig. 2, partial inhibition of growth of most of the strains by these two antibiotics was accomplished by concentrations which failed to inhibit any of the strains completely.

The therapeutic significance of partial inhibition of diphtheria bacilli is not clear. A comparison of the differences among the antibiotics with respect to the

range of partial inhibition, as shown in Fig. 2, is nevertheless of interest. Bacitracin exerts almost no inhibitory effect in concentrations lower than those required for complete inhibition, whereas streptomycin, aureomycin, and Terramycin exert marked inhibition of more than two-thirds of the strains over a four- to eightfold range of concentrations below those which are necessary for complete inhibition of any of the strains.

If in Fig. 2 one were to draw a vertical line from the end of each of the curves which represent partial inhibiting concentrations to the corresponding curve of complete inhibitory concentrations, the result would make possible a division of the antibiotics into two groups. The first group would include bacitracin, aerosporin, Chloromycetin, and penicillin. The concentrations of these antibiotics which partially inhibit 100 per cent of the strains also produce complete inhibition of all of the strains in the case of bacitracin and 97, 80, and 67 per cent of the strains in the case of aerosporin, Chloromycetin, and penicillin, respectively. The remaining antibiotics would constitute the second group; the concentrations of these agents which partially inhibit all of the strains produce complete inhibition of 28 per cent of strains in the case of streptomycin and neomycin and of only 14 and 3 per cent with Terramycin and aureomycin, respectively. For the first group of agents only a twofold or fourfold increase in concentration beyond that required for partial inhibition is necessary to produce complete inhibition, while an eightfold to sixteen fold increase is necessary to produce the same effect with the second group of antibiotics.

In the case of aureomycin, the curves for partial and complete inhibition parallel one another along their entire length. Uniform and rapid deterioration of this drug at 37° C. is responsible, in part, for the wide separation of these curves. The reasons for the divergence of the curves representing partial and complete inhibition of the other antibiotics are not clear.

The comparative sensitivity of the offending organism is only one of the major factors which determine the choice of antibiotic for therapy in any given infection. The toxicity of the agent, of course, may be the determining factor. In addition, differences in attainable plasma levels, plasma-tissue concentration gradients, penetration into the tissue sites where the organisms are alive and multiplying, deterioration and inactivation in vivo and in the rate of excretion must also play important roles. In general, it is probably necessary to maintain inhibiting concentrations of antibiotic at the site of infection for varying periods depending on the rate at which the particular organisms are destroyed at those concentrations and this is obviously difficult to determine in vivo. However, concentrations corresponding to the values for sensitivity obtained in this study, since they are generally higher than those obtained by most other methods, should be effective if they could be maintained in the infected tissues.

With these considerations in mind, aerosporin and polymyxin may be classified as totally unsuited for therapeutic purposes. The use of bacitracin, in spite of its marked in vitro activity, and also of neomycin would have to be limited to local applications because of the toxicity of these agents when given

parenterally. The concentrations required for in vitro inhibition by penicillin, Terramycin, Chloromycetin, aureomycin, and streptomycin could be maintained in plasma and they may all have therapeutic potentialities.

In the course of treatment of a few patients it was observed that virulent diphtheria bacilli in throat cultures were sometimes replaced by avirulent *mitis* strains following penicillin therapy. Sensitivity tests showed that the latter strains did not differ significantly in their in vitro sensitivity from the virulent strains that had been isolated prior to therapy.

No attempt has been made to demonstrate any activity of antibiotics against the exotoxin of *C. diphtheriae*. Previous reports[8, 9] have indicated that penicillin has no effect on diphtheria toxin which is responsible for the serious manifestations of the disease. It is emphasized, therefore, that antibiotic therapy is not a substitute for antitoxin in the treatment of acute diphtheria. It may, however, be useful in the prevention and treatment of diphtheria carriers.[10]

SUMMARY

Thirty-six virulent strains of *C. diphtheriae* and thirteen other strains of Corynebacterium were tested for sensitivity to nine antibiotics in vitro. An "antibiotic spectrum" for virulent diphtheria bacilli was constructed from the results of these tests. On a weight basis the order of activity of these antibiotics was as follows: (1) bacitracin, (2) penicillin, (3) Terramycin, (4) Chloromycetin, (5) neomycin, (6) aureomycin, (7) streptomycin, (8) aerosporin, and (9) polymyxin. The activity of penicillin and bacitracin was essentially the same and was significantly greater than that of the other agents. Aerosporin and polymyxin were essentially inactive. The other five antibiotics were about equally active. The antibiotics varied considerably with respect to the range of concentrations over which partial inhibition of growth was demonstrable.

The significance of these findings was discussed.

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USE OF NEO-SYNEPHRINE IN PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

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IN SO FAR as we have been able to determine, the use of Neo-Synephrine in stopping attacks of paroxysmal supraventricular tachycardia has not been reported in the pediatric literature. It seems worth while, therefore, to report our experience with a case of recurrent paroxysmal supraventricular tachycardia using intravenous Neo-Synephrine in which other forms of standard therapy had been tried previously.

A recent large survey of 5,600 children[1] revealed only 0.09 per cent with paroxysmal tachycardia, so it is a relatively rare clinical manifestation in infants and small children.

For some years digitalis, quinidine, acetylcholine bromide, and Prostigmine have been standard drugs in the physician's armamentarium,[2] in addition to, or along with, mechanical methods for the treatment of paroxysmal tachycardia. Intravenous Neo-Synephrine has been used successfully in paroxysmal auricular tachycardia in adults.[3] The effective mechanism involved is believed to be the simultaneous stimulation of the cardiac inhibitory centers: i.e., carotid sinus and aortic arch, by the sudden elevation of the blood pressure. The combination of action of these cardiac inhibitory centers has been found to be more than adequate to counteract the mild stimulating influence of Neo-Synephrine on the sinoauricular node.[3]

CASE REPORT

C. L. S., a 27-month-old white male child, was admitted to Louisville General Hospital on Feb. 28, 1950, with the chief complaints of pulsations in the neck, fever, cold, and weakness.

Present Illness.—The patient had developed a slight cold two days prior to admission with cough, watery nasal discharge, and slight fever. At 8 A.M. on the morning of admission the child's mother noticed rapid pulsations in his neck, which she had learned through experience were due to an attack of tachycardia.

Past History.—The patient had been delivered at Louisville General Hospital by low forceps on Nov. 24, 1947, weighing 3,800 grams. The mother was a primipara aged 20 years, who had uneventful prenatal and postnatal periods. The patient was discharged with his mother on the fourth post-partum day as a normal infant.

On Jan. 18, 1948, at two months of age, the patient was admitted to the Pediatric Department of the hospital with the chief complaint of "blue spells" which would last two to three hours. There was a history of a cold for one week prior to admission. The temperature was 100.2° F., respirations 30, and pulse 156. The infant was very slightly cyanotic with mild substernal and

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subcostal retraction and bilateral wheezing on auscultation. An x-ray of the chest revealed a large mass in the superior mediastinum which was reported to be thymus. All symptoms disappeared rapidly after radiation of the thymus with 78 *r*'s for three minutes, and the infant was discharged Jan. 25, 1948.

The patient was next seen at the age of 8 months on Aug. 12, 1948, at which time he was admitted to the hospital with the chief complaints of "turn-

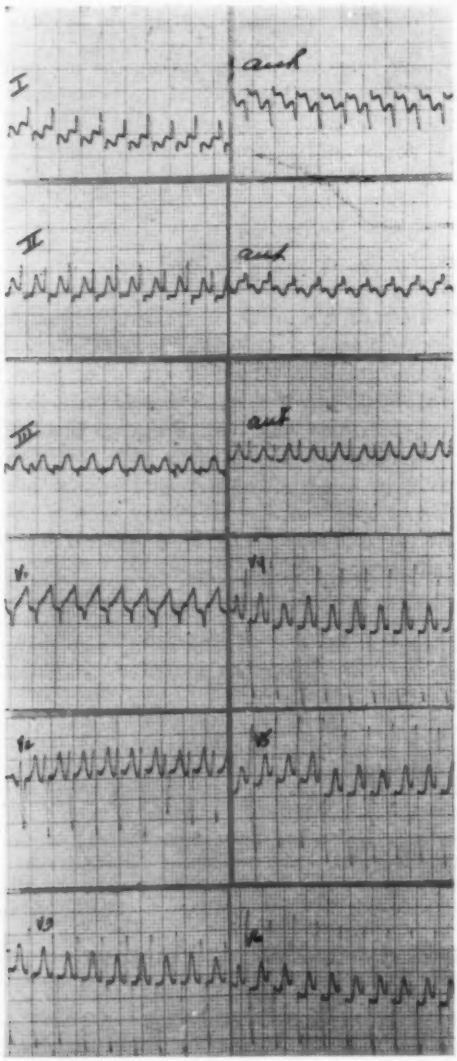

Fig. 1.—Abnormal electrocardiogram of C. L. S. Rate, 290 plus. Rhythm, supraventricular tachycardia. Acute coronary insufficiency.

ing blue" and "choking spells." He had gotten along fine after his first admission for two months, but then began to have brief periods of cyanosis with difficulty in breathing which had become progressively more pronounced and frequent. Developmental history was normal with the child sitting alone at 6 months of age. On physical examination the child was slightly cyanotic when crying. The heart rate was 160 to 180 and the liver was palpable 4 cm. below the right costal margin. The blood Kahn was negative. The chest film was normal. The red blood cell count was 2,200,000, hemoglobin 7.5 Gm., white blood cells 8,400 with 63 per cent neutrophiles and 37 per cent lymphocytes. The electrocardiogram showed auricular tachycardia with a rate of 290. The tachycardia failed to respond to carotid pressure, eyeball pressure, oxygen, or Prostigmine. However, the rate slowed to 120 on administration of 0.2 mg. acetylcholine bromide, after which the electrocardiogram showed high, peaked P waves with sinus tachycardia, a regular rhythm, and right axis shift. The rate remained down during the remainder of this hospital period and he was discharged Aug. 17, 1948, with a diagnosis of (1) auricular paroxysmal tachycardia and (2) congenital heart disease, incompletely diagnosed.

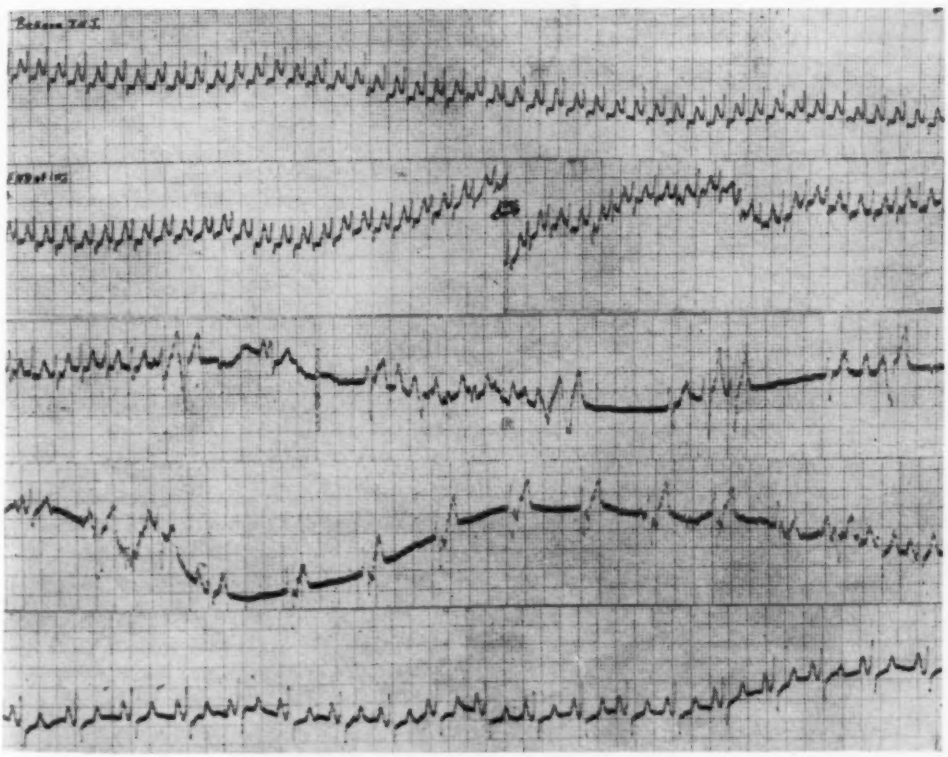

Fig. 2.—Line one represents the electrocardiogram before and during the injection of Neo-Synephrine, which ends at the beginning of line two. In the center of line two, 3 seconds are omitted to save space. The remaining three and one-half lines show what happened on the electrocardiogram as the action of Neo-Synephrine slowed the heart rate.

On Aug. 30, 1948, the patient was readmitted in an attack that failed to respond to Prostigmine or acetylcholine bromide. He was rapidly digitalized and the rate dropped to 88. It rose again slowly to 200 within three days but at this point quinidine sulfate was started in doses of 16 mg. every twelve hours, and the rate dropped to 72 on a combination of these drugs.

The patient was followed in the Out-Patient Clinic of the hospital and was free from attacks until Feb. 15, 1950, with the exception of a bout of tachycardia

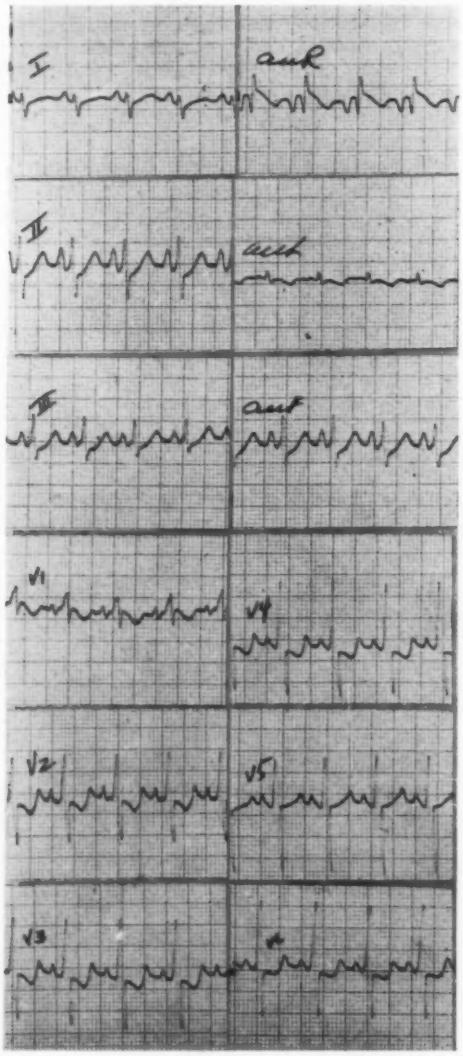

Fig. 3.—Abnormal electrocardiogram showing right heart strain, acute coronary insufficiency, and abnormality of P waves. Rate, 126 plus. Rhythm, sinus tachycardia.

accompanying bronchopneumonia in July, 1949. On Feb. 15, 1950, he was admitted to the hospital with tonsillitis and a heart rate of 250. Temperature was 102.4° F. and respirations were 24. On physical examination the tonsils were 2 plus hypertrophied and injected. The liver was 4 cm. below the right costal margin. There was a Grade 2 systolic murmur in the third interspace just to the left of the sternum, not transmitted. There was no thrill and no cardiac enlargement to percussion. A chest film revealed bilateral early bronchopneumonia. Urinalysis was normal. The red blood cell count was 3,900,000 with 9 Gm. hemoglobin. The white blood cell count was 9,350 with 83 per cent neutrophiles, 15 per cent lymphocytes, and 2 per cent eosinophiles. The electrocardiogram showed a tachycardia of 240 with a right heart strain and acute myocardial insufficiency. It was decided to try the patient on intravenous Neo-Synephrine, and 0.3 mg. was injected. Within ninety seconds the heart sounds seemed to skip several beats by auscultation and then instantly reverted to a rate of 100. Immediately after this the electrocardiogram showed the rate to be 116, a right heart strain, high peaked P waves, and myocardial ischemia. The rate remained down and the patient was discharged Feb. 19, 1950.

At the next admission the temperature was 100.6° F., pulse 300, respirations 38, blood pressure 110/80, weight 13.2 kg. Physical examination showed a poorly developed but fairly well-nourished child who appeared in mild distress and somewhat apprehensive. The liver was palpable one centimeter below the right costal margin. Laboratory work at this time showed a red blood cell count of 4,000,000 with 10 Gm. hemoglobin, a white blood cell count of 22, 150, with 72 per cent neutrophiles and 28 per cent lymphocytes. The urinalysis was negative. A six-foot chest film was normal. Cardiac fluoroscopy was normal. An electrocardiogram taken at this admission is reproduced by photograph in Fig. 1. It was decided to attempt to repeat our results obtained previously with Neo-Synephrine, taking electrocardiograph readings during the administration. The resulting electrocardiogram is shown in Fig. 2. The Neo-Synephrine dose was again 0.3 mg. given intravenously. Fig. 3 shows the electrocardiogram tracing taken forty-eight hours after the heart rate had been slowed by the Neo-Synephrine. On March 13, 1950, the patient suffered another attack of tachycardia. At this time 0.1 mg. and 0.2 mg. of Neo-Synephrine were given intravenously at intervals of fifteen to twenty minutes with no effect. However, on injecting the usual dose of 0.3 mg., the rate of 220 reverted to a rate of 92 within three minutes.

COMMENT

Reports of recurrent attacks of paroxysmal tachycardia in infants have appeared in the literature,[4-6] but we believe this case more closely resembles one reported by Limper.[7] To date we have been unable to determine in this case the exact cardiac pathology to which the tachycardia might be attributed. However, we postulate some congenital cardiac disease, probably an interauricular septal defect.

In this case intravenous Neo-Synephrine was of benefit each time it was used, while the result of using the standard drugs could not be predicted. We do not advocate the discarding of any of the medications that have withstood the test of time, but wish to add Neo-Synephrine to the list of readily available therapeutic agents for paroxysmal tachycardia. In view of the apparent transitory cardiac arrest demonstrated by the electrocardiogram in Fig. 2, we believe that this drug must be given with some discretion as to dosage. A safe

initial dose seems to be 0.1 mg. and this can be increased by 0.1 mg. at intervals of thirty minutes to as high as 0.5 mg.

CONCLUSION

Intravenous Neo-Synephrine has been shown to be effective in rapidly controlling an attack of recurrent paroxysmal supraventricular tachycardia. Reasonable discretion must be used in determining the safe dosage.

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THE EFFECT OF ADRENOCORTICOTROPIC HORMONE IN EPILEPSY

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THIS study of the action of adrenocorticotropic hormone (hereinafter called ACTH) and adrenal-like hormones in epilepsy was stimulated in two ways. First, it occurred to us that ACTH administration produced a metabolic state superficially similar to that produced by a ketogenic diet, which Keith,[1] Livingston[2] and others have shown to be beneficial in epilepsy. Second, cortisone and ACTH have been shown to alter the electroencephalogram in conditions other than epilepsy. Thorn[3] reported that the abnormally slow brain wave seen in patients with Addison's disease was changed to normal after treatment with cortisone but not with desoxycorticosterone acetate (hereinafter called DOC). Hoefer[4] showed that after treatment with ACTH abnormal brain wave tracings appeared in patients who had had normal tracings before treatment.

After embarking upon this study, it came to our attention that, in 1942, McQuarrie[5] had reported beneficial effects in two patients with epilepsy who had been treated with DOC. Electroencephalograms were not done in these patients.

MATERIALS AND METHODS

The six children were all patients of the epilepsy clinic of the Johns Hopkins Hospital. They were admitted to the metabolism ward of the Harriet Lane Home for this study. They had all been treated continuously with anticonvulsant medication for at least six months prior to admission to the hospital with one exception. This patient, J. M., had received no regular medication for the month prior to admission. In each case the anticonvulsant drug or drugs that had been administered was continued throughout the study. Electroencephalograms were obtained on the day of admission to the hospital in all but one case. This patient, M. V., had had numerous previous brain wave studies, the last of which had been one month before admission to the hospital.

Sodium and potassium in the blood and urine were measured by the flame photometer. The intakes of these ions were estimated from conventional tables. In five cases measurements were made of the sodium and potassium excretion in the urine. Four of these five patients were given a constant diet which was taken well. The fifth took his diet irregularly.

Urinary steroids were measured by methods previously reported.[6] Eosinophiles in the blood were counted by the method of Randolph.[7]

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This work was partly supported by a grant from the American Cancer Society for studies on the relationship of the pituitary hormones, thyroid hormone, and the steroid hormones of the adrenal glands and gonads to normal and abnormal growth, and by a grant from the Commonwealth Fund for the study of endocrine problems in childhood.

The ACTH* dosages listed are those of the original assay by the Armour Laboratories. ACTH and cortisone were administered in divided intramuscular dose at four-hour intervals. DOC was given in a single injection at the beginning of each daily period.

CASE REPORTS

CASE 1.—M. V. was a 13-year-old boy who had had his first convulsion at the age of 2½ years. Since that time he had had frequent grand mal spells. Over the last few years before the present study he had had many petit mal and psychomotor spells. After trials with many medications his grand mal seizures were finally controlled wth Dilantin and Mebaral. At the time of admission to the hospital he had not had any major convulsions for many months, but he was having daily petit mal and psychomotor spells. An EEG one month before admission to the Harriet Lane Home showed, as had many previous tracings, paroxysmal bursts of high voltage, slow spike and wave forms (petit mal variant). There were sixteen such paroxysmal bursts in the tracing which was carried out for twenty minutes. The high voltage spikes and waves were present both during rest and during hyperventilation.

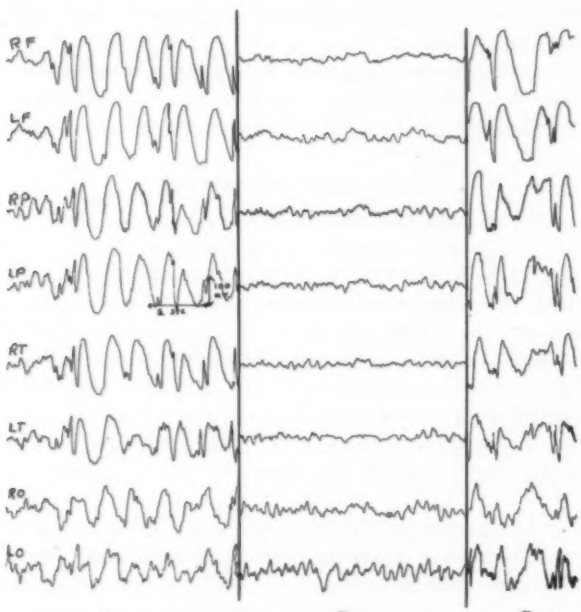

Fig. 1.—*A*, Sample of EEG of Patient M. V., after four days of DOC treatment; *B*, after ten days of ACTH treatment, *C*, one month after the end of ACTH treatment.

While in the hospital he received Dilantin and Mebaral just as he had previously. Fifteen milligrams of DOC were given each day for four days. This produced a marked sodium retention as expected. During this period there was no change in his spells. At the end of this period another EEG was

*Kindly supplied by Dr. John R. Mote, Armour Laboratories, Chicago, Ill.

essentially the same as the previous tracing (Fig. 1*A*). He had a marked sodium diuresis when DOC was discontinued. Four days later he was given ACTH 100 mg. a day for eleven days. After three days of therapy no more spells occurred until four days after ACTH was discontinued. However, during his hospital stay prior to receiving ACTH he had had an average of only one observed spell every other day. At least half of his minor spells could have gone unobserved throughout his hospitalization. It is safe to say that he had none of the more severe spells after the third day of ACTH treatment. An EEG taken after four days of ACTH therapy showed eight bursts of slow spike and wave forms in a twenty-minute record. Another tracing after seven days of treatment showed four bursts of paroxysmal high voltage spike and waves in twenty minutes. At the end of therapy with ACTH an EEG demonstrated a brain wave pattern consisting in runs of 6 per second waves, 7½ to 8 per second waves and some runs of low voltage, fast activity. There were no slow spike and wave forms in the entire twenty-minute tracing (Fig. 1*B*).

While receiving ACTH the patient's sodium retention was even greater than when he received DOC, and this continued throughout the period of treatment. A profound sodium and water diuresis occurred after cessation of ACTH treatment, and 4.5 kg. of weight were lost in five days. In the month following discharge he had no major attacks and his mother thought his minor attacks were less frequent. An EEG taken twenty-four days after ACTH treatment was discontinued showed regression toward the state before treatment with many high voltage, slow spike and wave forms (Fig. 1*C*).

CASE 2.—G. G. was a 4½-year-old girl who had had the first of a series of left-sided clonic convulsions at 3½ months of age. When she was 2 years old she began to have right-sided convulsions as well. Since that time, she had had akinetic petit mal spells as well. Dilantin, bromides, phenobarbital, and Tridione had all been tried. For the year and a half before this study she had been treated with 3 gr. Mebaral a day and had received 15 c.c. t.i.d. of a mixture containing 5 Gm. of potassium bromide, 60 c.c. of glycerol, and water to make 180 c.c. She had had an average of two to three convulsions a week on this regimen. However, there were occasionally as many as seven convulsions in one day and at other times intervals of two to three weeks without any major seizures. She had frequent akinetic petit mal spells throughout this period. An EEG taken on the day of admission to the hospital showed short paroxysmal bursts of very high voltage 3 per second waves in all leads. There were random spikes between these high voltage waves. Fifteen such paroxysmal bursts appeared during the twenty-minute tracing (Fig. 2*A*). While in the hospital she continued to receive Mebaral and bromides. She was given ACTH 40 mg. a day for four days followed by 80 mg. per day for three days. An EEG after four days of treatment showed essentially no change. However, after seven days of treatment her EEG did not show any 3 per second waves or spike forms in a twenty-minute tracing (Fig. 2*B*). She remained in the hospital eight days after ACTH was discontinued and EEG's made five and seven days after treatment showed no regression toward her pretreatment state. She had no attacks in the hospital and seemed much more alert and bright after treatment. Her speech became more understandable. Twelve days after ACTH was discontinued she had an akinetic spell lasting one and one-half minutes. She had two severe generalized grand mal attacks, one seventeen and one twenty days after withdrawal of ACTH. Her parents reported that she was calmer and better behaved and coordinated, brighter, and spoke better after her hospitalization. They stated voluntarily that this was so noticeable that the neighbors had commented upon it. An EEG fourteen days after ACTH had been stopped once more showed

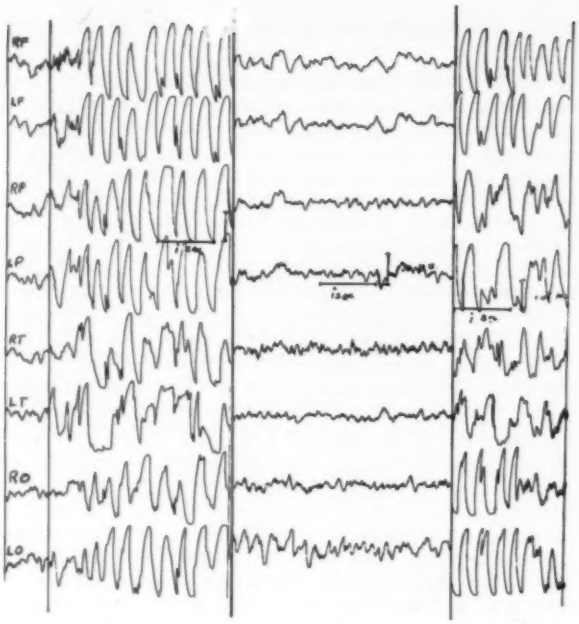

Fig. 2.—*A*, Sample of EEG of Patient G. G. on admission to hospital; *B*, after seven days of ACTH treatment; *C*, fourteen days after the end of ACTH treatment.

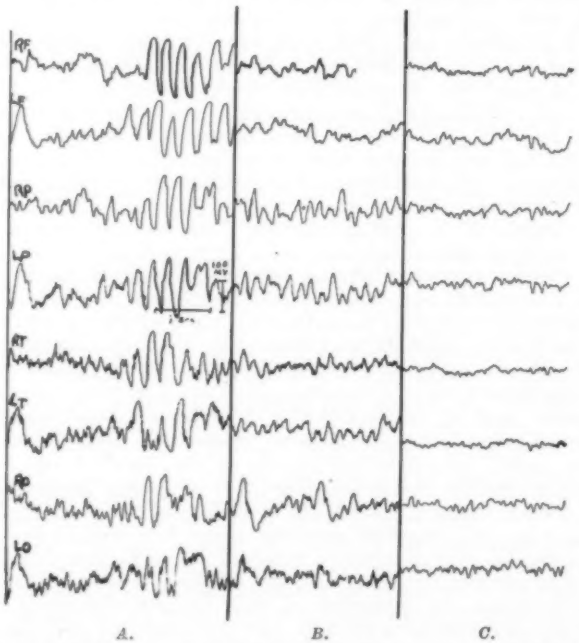

Fig. 3.—*A*, Sample of EEG of Patient G. G. after receiving 5 mg. of DOC for four days; *B*, four days after cessation of treatment with DOC; *C*, after receiving a ketogenic diet for ten days.

paroxysmal bursts of high voltage 3 per second waves with random spikes between these waves. There were six such bursts in twenty minutes (Fig. 2*C*). An EEG ten days later showed ten such bursts. The patient was then readmitted to the hospital and given 5 mg. of DOC a day for four days. At the end of this time an EEG demonstrated only one paroxysmal burst of high voltage 3 per second waves in twenty minutes (Fig. 3*A*). There was a definite sodium retention while she received DOC followed by a diuresis on withdrawal. This was unaccompanied by any marked weight change. An EEG four days after DOC was withdrawn showed an almost constant run of 4 to 5 per second waves although there were no paroxysmal bursts of 3 per second high voltage waves (Fig. 3*B*). She was then given 1 mg. of DOC per day for four days. For the first two days she seemed to retain insignificant amounts of sodium, but after this there was a normal level of excretion of sodium for the last two days she received the small dose of DOC. An EEG taken after four days of the smaller dose of DOC showed no change from the previous tracing. She was then placed on a starvation regime followed by a ketogenic diet. Her EEG after eleven days of a ketogenic diet was essentially normal (Fig. 3*C*). She had no attacks in the hospital and was entirely well for four months following discharge. Since then she has had infrequent convulsions.

Case 3.—L. McC. was a 12-year-old girl who had had a single tonic convulsion of unknown etiology at 11 months of age. At 13 months she had had two or three short clonic convulsions associated with a temperature of 102° F. She was then well till 6 years of age when she began to have frequent psychomotor seizures. In the year before admission these occurred from one to seven

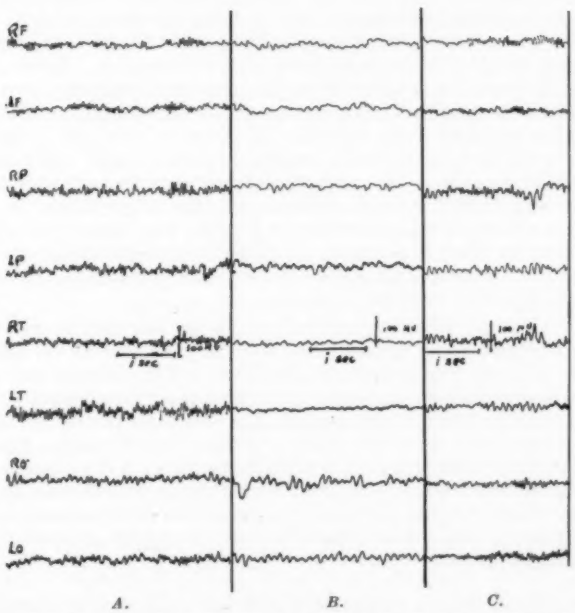

Fig. 4.—*A*, Sample of EEG of Patient L. McC. taken on day of admission to hospital; *B*, after five days of ACTH administration; *C*, twenty-four days after the end of ACTH treatment.

times a day but frequently there were intervals of several weeks between attacks. She was given Mesantoin and Tridione without benefit during this period. Eight weeks before entry Tridione was stopped. On admission to the hospital an EEG showed an abnormal brain wave pattern with abnormally fast (18 to 20 per second) waves (Fig. 4*A*). She continued to receive Mesantoin to the end of her hospital stay. She was given ACTH 50 mg. per day for seven days. She had two observed spells in the week she was in the hospital. An EEG after two days of treatment showed no change. One after five days showed low voltage, fast activity in temporal leads and fairly regular 8 to 9 per second waves in other leads (Fig. 4*B*). Another EEG five days after treatment with ACTH was stopped showed fairly regular 7 to 8 per second waves in both occipital leads with low voltage, fast activity and some 8 to 9 per second waves in all other leads. At discharge from the hospital her medication was changed from Mesantoin to Phenurone. Her EEG began to show reversion to its former state nine days after discontinuing ACTH. At this time there were runs of 17 to 18 per second waves in the frontal leads and long runs of 20 per second waves in the occipital leads (Fig. 4*C*). Her stepmother volunteered that her disposition was much improved, and she was active and pleasant for about a month following hospitalization. Then she reverted to her former retiring and more complaining personality although her spells were no more frequent. She did well while receiving Phenurone, having only two spells in the month following discharge from the hospital. We were unable to follow the patient any longer.

CASE 4.—J. O. was a 4½-year-old boy who had had frequent generalized convulsions for the year and a half before this study. Attacks occurred most often in the afternoon and evening. He had had ten to thirty attacks a day until six months before admission to the hospital when he was first seen in the epilepsy clinic of the Johns Hopkins Hospital. At this time treatment with Nuvarone (3 methyl 5 phenyl hydantoin)* was begun. Since then he had had only two to three attacks each night. These lasted only about one minute and all occurred in the first few hours he was asleep. It is possible that he had others after his parents went to bed. An EEG was taken on the day of admission to the Harriet Lane Home which showed a brain wave pattern essentially normal for his age. He continued to receive Nuvarone throughout this study. He was given 80 mg. of ACTH a day for seven days. In the hospital he had two or three convulsions nightly for the two nights before ACTH was begun and for the first two nights of ACTH administration. Thereafter he had only one short convulsion in the last five days of treatment. EEG's during this period showed no significant change.

One day after ACTH was stopped, while he was still receiving Nuvarone at home, he had two convulsions. The next day he had forty, and the following day 100. He was readmitted to the Harriet Lane Home and observed for two and one-half days. He had no convulsions the first night, but five occurred the next day and twenty the following. He was then fasted for four days and then given a ketogenic diet. He had no convulsions five days after the beginning of the period of fasting. After ten days, however, he began to have one to two convulsions a night. This continued till he was discharged one month later. Since discharge his family have seen no convulsions during the five-month follow-up period. There has been no change in electroencephalograph tracings during this time.

CASE 5.—M. S. was a 13-year-old girl who had had petit mal epilepsy of the simple staring type for three and one-half years. Menarche had been at

*Kindly supplied by Drs. Everett and Richards of Abbott Laboratories.

the age of 9 years. She had been treated with Tridione, phenobarbital, Phenurone, and Dilantin at various times. At the time of this study she had been taking Paradione for two years and had averaged ten spells a day with premenstrual exacerbations. An EEG on admission to the hospital showed paroxysmal bursts of typical 3 per second spike and wave forms. Ten such paroxysms were seen in a ten-minute tracing. They were present both during rest and during hyperventilation. Paradione was continued during and after hospitalization. She was given 50 mg. of ACTH a day for five days, 80 mg. for one day, and 110 mg. for one day. She had very infrequent spells in the hospital but she had begun to menstruate the day ACTH was started, and, in addition, hospitalization itself probably had a therapeutic effect in her case. After ACTH had been given for three or four days clinical petit mal attacks could not be elicited by three minutes of hyperventilation. However, an EEG after treatment showed no change although bursts of 3 per second spike and wave forms were less frequent. ACTH caused sodium retention for two days followed by a sodium diuresis while the drug was still being administered. This patient has done fairly well since discharge from the hospital largely due to psychologic help she has received.

CASE 6.—J. M. was a 7½-year-old girl who had been apparently well until four months before admission to the hospital when she had her first generalized convulsion. This was unassociated with fever, trauma, etc. It lasted between five and ten minutes. She had two similar attacks in the following six weeks. Dilantin was started but was stopped one month before admission when she began to have twenty to forty generalized convulsions a day. At this time she was noted to be having frequent petit mal spells as well. At the time of admission she was receiving no regular medication. While in the hospital she received only small sporadic doses of phenobarbital in addition to the ACTH, DOC, and cortisone employed in this study. An EEG taken on the day of admission showed an abnormally slow brain wave pattern with many very high voltage 1 per second waves (Fig. 5*A*). She was given DOC 5 mg. a day for two days and 10 mg. a day for two days. Her EEG after this was unchanged. She seemed to have more severe convulsions on withdrawal of DOC coincident with a marked sodium diuresis, but certainly had no more attacks than when receiving this medication. In the five days in the hospital before DOC was given she had an average of thirty seizures a day. During the four days DOC was given she had an average of thirty-five attacks a day, and during the three days after this she had twenty-nine attacks each day. She was then given 100 mg. of cortisone a day for seven days. An EEG after four days of cortisone therapy showed many 1½ to 2 per second high voltage waves. Another at the end of the treatment period showed no further change. Cortisone treatment was associated with a change in personality so that she became very withdrawn, refused to talk to the doctors, and no longer played with the other children on the ward. During this period she averaged eighteen seizures a day but had thirty on the last day of treatment. She was then given ACTH 100 mg. a day for four days. She may have been improving on this treatment. There was an average of twenty-five convulsions per day but their incidence was declining progressively to a low of eleven on the last day of treatment. However, ACTH therapy had to be discontinued because she had become alternately withdrawn and overactive and she showed continuous, purposeless, choreiform movements and no longer could sit without support or brush her teeth. An EEG at this time was not significantly changed from previous tracings (Fig. 5*B*). Starvation was begun immediately, preparatory to giving her a ketogenic diet. After four days of starvation and one day on a ketogenic diet she had no more convulsions for the remaining sixteen days in

the hospital. Her choreiform movements and abnormal personality disappeared in about five days after ACTH was discontinued, but she was not able to sit up by herself or walk for another ten days. An EEG after ten days of this regimen showed an essentially normal tracing (Fig. 5*C*). In the three months following discharge from the hospital she had no spells. An EEG at the end of this time was still essentially normal.

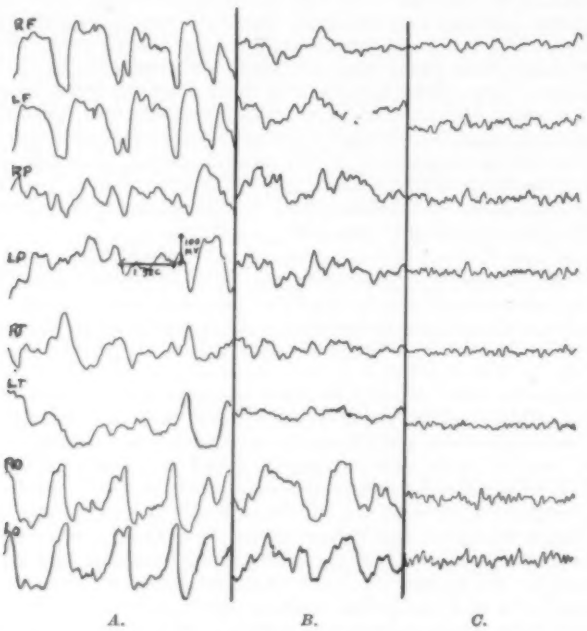

Fig. 5.—*A*, Sample of EEG of Patient J. M. taken on day of admission to hospital; *B*, at the end of four days of treatment with ACTH; *C*, after receiving a ketogenic diet for eleven days.

RESULTS

The expected increase in urinary 17-ketosteroid and neutral reducing lipids was demonstrated in all patients receiving ACTH. This was accompanied by the usual eosinopenia. At no time was there a significant change in serum electrolyte levels in any of the patients receiving ACTH, DOC, or cortisone. No patient showed a significant weight gain while getting any of these drugs, although one, M. V., lost 4.5 kg. on withdrawal of ACTH. No patient showed any acetonuria or glycosuria while receiving these drugs.

Of the six children treated with these hormones, four were objectively benefited when treated with ACTH. The one patient with simple petit mal, M. S., showed no definite improvement, and treatment was considered a failure. The other patient, J. M., who was not relieved by treatment, received apparently adequate amounts of DOC and cortisone, but ACTH had to be stopped after four days because of unfortunate side effects. This patient was

then given a ketogenic diet; she had no more convulsions and her EEG became normal. The patients who did respond to ACTH demonstrated many types of brain waves and clinical manifestations of epilepsy. Some had grand mal with or without petit mal, and/or psychomotor spells. One had only psychomotor seizures. One other patient had frequent grand mal seizures which stopped while he was receiving ACTH. This patient had an essentially normal EEG before and after treatment. When treatment was stopped this patient became immediately much worse than he had been before he received ACTH. The following abnormalities in EEG disappeared on therapy with ACTH: slow spike and wave forms, abnormally fast activity, and abnormally slow waves. One patient whose EEG improved with ACTH also showed a more temporary improvement with DOC.

The improvement achieved lasted for varying lengths of time. One patient, J. O., had a clinical relapse in one day. The improvement in EEG pattern lasted for periods up to two weeks. No certain clinical benefit could be demonstrated for any significant period after the drug was withdrawn. Clinical improvement was difficult to evaluate but in no instance did the clinical course run contrary to the changes in the EEG.

Only one of these patients, J. M., was treated without simultaneous treatment with ordinary anticonvulsant agents.

DISCUSSION

This study has raised the problem as to how the beneficial effects of ACTH are produced in epilepsy. Is this benefit solely the result of changes in electrolyte balances and concentrations? McQuarrie[5] felt that the clinical benefit obtained in his patients was produced by changes in the intracellular concentrations of sodium, potassium, and water. In the balance study he reported there was no significant over-all sodium retention since the patient was on a low salt diet.

One patient, M. V., herein reported, responded to ACTH but not to DOC. However, ACTH was given to him for a longer period of time than was DOC. One patient, G. G., responded to DOC as well as to ACTH. Her response to DOC did not seem as long or as good but one cannot compare the dosages of these drugs. The improvement in McQuarrie's patients was immediate, occurring the day after DOC was started, while in our patients improvement was not evident for at least four days after ACTH was started.

We believe, but cannot be sure from this preliminary work, that there is some beneficial action of adrenal hormones in epilepsy beyond their effect on electrolyte metabolism. This, we believe, is due to the known effect on carbohydrate, protein, and fat metabolism of the corticosteroid type of hormone.

SUMMARY

The effects of ACTH, DOC, and cortisone have been studied in six children with epilepsy. In four of these ACTH produced improvement in the EEG or in the clinical condition. DOC had a beneficial effect on the brain wave in one of the two patients given this drug.

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TESTOSTERONE IN PROGRESSIVE PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY

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IN ADDITION to affecting secondary sex characteristics, testosterone propionate or methyl testosterone has been shown to increase the mass of skeletal muscle[1] when administered to human beings.[2, 3] It has also been demonstrated that subjects receiving testosterone propionate excrete less urinary nitrogen and creatine.[2]

Such observations suggested the possible value of testosterone in diseases characterized by muscular weakness, muscular wasting, and creatinuria. Progressive pseudohypertrophic muscular dystrophy is such a disease and is one in which all attempts at therapy to date have been unsatisfactory.

Consideration of the following points suggested that steroids of the testosterone group might conceivably be involved in the genesis of the disease, and therefore a clinical therapeutic trial was in order:

1. Progressive pseudohypertrophic muscular dystrophy occurs almost exclusively in males.[4]

2. The disease occurs primarily in children when androgen production is minimal.[5]

3. When it does affect adults, the progress of the disease is slower than in children (who have less androgen secretion).[4, 5]

4. Muscle mass and strength decrease as the disease advances.

5. Creatinuria is increased in progressive pseudohypertrophic muscular dystrophy.[6]

6. Testosterone decreases creatine excretion in progressive pseudohypertrophy muscular dystrophy.

Our observations corroborate the report of Hoagland, Gilder, and Shank[6] that methyl testosterone and testosterone propionate do not halt the course of progressive pseudohypertrophic muscular dystrophy.

MATERIAL AND METHOD

Eleven boys (aged 7 to 14 years) with progressive pseudohypertrophic muscular dystrophy were selected at random for this study from the Pediatric Neurology Clinics of the Cook County and Michael Reese Hospitals. In each case the diagnosis, made on the basis of the clinical history and physical examination, was confirmed by muscle biopsy. The patients' symptoms had not been relieved by other forms of therapy (Prostigmine, vitamin E, pyridoxine, gelatin, glycine) prior to this study.

From the Children's Neurology Clinics of the Cook County Hospital and of the Michael Reese Hospital.

The patients and their parents reported their subjective evaluation of the progress of the disease. In addition, objective methods for judging the course of the disease were employed. Muscle strength was measured by a spring dynamometer which registered (in pounds) the pull of each muscle group tested.* Table I lists a typical dynamometer study. The registration of a five-pound difference in pull in two tests by any muscle group appeared to indicate a significant change in the strength of that muscle group. It should be borne in mind that sudden increases in isolated muscle groups which are noted in the early testing period may be the result either of faulty testing or a tired patient on the earlier test, or may represent a gain in muscle strength which is due to exercise

TABLE I. DYNAMOMETER STUDIES IN CASE 4 (IN POUNDS OF PRESSURE RESISTED)

		4/26/43	5/28/43	9/23/43	1/6/44	CHANGE PLUS OR MINUS
Right foot	Plantar flexion	14	12	14	11	− 3
	Dorsiflexion	10	10	12	12	+ 2
Left foot	Plantar flexion	15	14	18	11	− 4
	Dorsiflexion	10	18	11	13	+ 3
Right knee	Flexion	1	2	3	3	+ 2
	Extension	1½	2	2	1½	0
Left knee	Flexion	1½	4	3	3	+ 1½
	Extension	1½	2	2	2	+ ½
Right hip	Flexion	2	6	4	2	0
	Extension	2	10	10	12	+10
	Abduction	3	3	3	4	+ 1
	Adduction	6	10	5	7	+ 1
Left hip	Flexion	1	6	4	2	+ 1
	Extension	2	10	10	7	+ 5
	Abduction	5	4	4	4	− 1
	Adduction	4	4	4	5	+ 1
Right shoulder	Flexion	14	18	12	13	− 1
	Extension	6	6	12	10	+ 4
	Abduction	16	16	18	22	+ 6
	Adduction	7	10	18	7	0
Left shoulder	Flexion	16½	18	16	12	− 4½
	Extension	10	8	8	8	− 2
	Abduction	16	17	18	21	+ 5
	Adduction	12	10	10	7	− 5
Right elbow	Flexion	17	17	17	18	+ 1
	Extension	6	6	9	15	+ 9
Left elbow	Flexion	19	18	16	15	− 4
	Extension	10	8	12	12	+ 2
Right wrist	Flexion	20	26	24	12	− 8
	Extension	17	22	18	9	− 8
	Ulnar deviation	14	19	16	14	0
	Radial deviation	15	12	14	15	0
Left wrist	Flexion	23	22	26	19	− 4
	Extension	13	20	18	7	− 6
	Ulnar deviation	12	17	18	13	+ 1
	Radial deviation	12	15	16	14	+ 2

*All tests were carried out by the same technique by Dr. C. O. Molander, Head of the Department of Physical Medicine, Michael Reese Hospital.

and not to the specific effects of the medication employed. It is obvious that even in normal muscle repeated exercise will also increase the strength of muscle to a certain point.

The patients also performed a simple procedure at home which tested functionally the muscles of the shoulder girdle, and also indicated roughly the progress of the disease. The patients were instructed to throw a one-pound bean bag daily as far as possible in overhand and underhand style, first with the right and then with the left arm. The distances were recorded. It was generally noted that there was improvement for several weeks following the institution of this test. This improvement in performance was interpreted as being due to improved skill rather than improved strength. After the improvement reached a plateau, testosterone administration was begun. This easy test provided the patient with an incentive to improve, and gave the physician more data than was obtainable from the less frequent dynamometer studies. The preliminary tests, performed for two to six months before methyl testosterone treatment began, were continued throughout the therapeutic trial period. Since the muscle groups in some individuals vary in demonstrable strength from day to day, the trend of such tests, rather than isolated readings, determined our interpretation of the progress of muscular strength.

A definite effect on secondary sex characteristics after methyl testosterone or testosterone propionate therapy was instituted indicated adequate biologic dosage. When painful erections or edema of the extremities occurred, the dose of methyl testosterone was decreased, and sodium chloride intake was limited.

RESULTS

Although in most instances the patients (and their parents) voluntarily reported initial subjective improvement and increased muscle strength, the dynamometer studies, bean bag throwing test, and subsequent clinical examinations failed to demonstrate any significant sustained improvement attributable to the therapy.

Table II groups the patients according to the duration of their symptoms, and includes pertinent clinical data as well as the schedule of therapy in each case.

Patient 1 improved initially with methyl testosterone* therapy. He was able to raise himself out of bed and walk around the ward with much less difficulty after six weeks of therapy. However, a biopsy, taken three months after therapy was begun, showed more interstitial fat than a similar biopsy taken four months previously. In spite of continued therapy, muscular weakness was progressive. The second patient in this group did not improve symptomatically, and his throwing ability deteriorated.

Although Patient 3 did not perform throwing tests, the dynamometer studies showed a marked decrease in the strength of the lower extremities. The arm and shoulder girdle muscles, although weak, did not demonstrate any

*The methyl testosterone (Metandren) for oral and sublingual administration was generously supplied by Dr. Ernst Oppenheimer, Ciba Pharmaceuticals, Inc., Summit, N. J.

TABLE II. SUMMARY OF RESULTS OF TESTOSTERONE THERAPY IN PROGRESSIVE PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY

PATIENT	AGE IN YEARS	DURATION OF SYMPTOMS	DAILY DOSAGE IN MG.	ADMINISTRATION		REMARKS
				ROUTE	DURATION IN MONTHS	
1	10	3 mo.	5	Inunction	1	Temporary clinical improvement
			10	Intramuscular	2	
			30	Oral	2	Regression in biopsy
			25	Intramuscular	2	
2	8	6 mo.	10	Oral	4	Testes normal in size No improvement
3	7½	3½ yr.	20	Oral	4	No improvement
			10	Oral	2	Marked priapism Personality change Ankle edema
4	7	4½ yr.	10	Oral	2	Temporary improvement
			5	Perlingual	2	Rate of progression slowed
			No Rx		3	
			5	Perlingual	3	
5	11	5 yr.	15	Inunction	3	Some exacerbation
6	14	7 yr.	5	Perlingual	8	Temporary improvement
7	8	8 yr.	5	Perlingual	9	Edema of ankles
			10	Perlingual	8	Feels better subjectively
8	13	8 yr.	5	Perlingual	6	Slight temporary improvement
9	10	9 yr.	5	Inunction	11	Exacerbation
10	12	9 yr.	20	Oral	4	Testes normal Parents note slight improvement Died after surgery
11	10	10 yr.	10	Oral	1	Bladder control established
			30	Oral	1	Temporary improvement
			20	Oral	3	Rate of progression slowed
			10	Oral	7	

significant change in power. While receiving 20 mg. of methyl testosterone daily, Patient 3 exhibited, in addition to the premature appearance of secondary sex characteristics, a marked change in personality. He became pugnacious, arrogant, and irritable at home and in school. Painful erections and marked ankle edema were noted six weeks after therapy was begun. These symptoms subsided when the dose of methyl testosterone was decreased to 10 mg. per day, and fluid and salt intake were limited.

Patient 4, aged 7 years, developed muscular weakness and had difficulty in walking at the age of 2½ years. The diagnosis of progressive pseudohypertrophic muscular dystrophy was confirmed by muscle biopsy. Large amounts of gelatin, vitamin B complex, and vitamin E did not alleviate his symptoms. Physical examination at the time of study revealed features characteristic of progressive pseudohypertrophic muscular dystrophy. The pectoral and shoulder girdle muscles were atrophic. The calves appeared hypertrophic. Lordosis was marked. The patient "climbed up himself" when arising from the supine posi-

tion, and had a waddling gait. Dynamometer studies prior to testosterone therapy indicated fair muscular strength. In the first four months of methyl testosterone therapy, the patient's ability to throw the one-pound bean bag was rather constant. Coincident with the cessation of therapy for three months, the patient's ability to throw underhand with his right arm diminished. This did not improve with the resumption of therapy. Over a period of nine months there was no demonstrable change in his capacity to throw the bag overhand with either arm and underhand with the left arm. Clinically, neither improvement nor deterioration was noted.

Patient 5 began to have erections four days after testosterone therapy was started, and muscle weakness seemed to increase more rapidly.

Among the patients whose symptoms had been present five years or more, only one (Patient 11) showed any objective improvement under methyl testosterone therapy. Patients 6 and 7 developed ankle edema which was not accompanied by cardiac failure or hypoproteinemia. Reducing the dose of sublingual methyl testosterone to 5 mg. every second day relieved the edema. Subjective improvement was noted in Patient 8, and some slight improvement in his general condition was observed. This, however, was not sustained. In Patient 9 no improvement at all was noted. As a matter of fact, it was felt that an exacerbation of symptoms followed the administration of therapy. In Patient 10 the parents noted a slight improvement in muscle strength, but this was not substantiated by dynamometer and functional studies. This patient died after surgery designed to release contractures at the knee.

Patient 11 was born with a spina bifida and the meningomyelocele was repaired at the age of 1 year. The diagnosis of progressive muscular dystrophy was considered when the patient was 7 years old, because muscular weakness was more widespread than would be expected from the cord lesion. Muscle biopsies of the upper and lower extremities revealed histologic changes characteristic of progressive pseudohypertrophic muscular dystrophy. Therapy with vitamin E, Prostigmine, and gelatin did not relieve the symptoms. When methyl testosterone was given, the mother reported that the patient "did not feel like dead weight" in her arms and that "his arms seemed to have more strength in them." Cessation of incontinence of urine and feces was noted after hormone therapy began. Dynamometer studies revealed no appreciable decrease in strength over a period of two and one-half years.

The facies of all the patients studied became adult in appearance, with the premature development of secondary sex characteristics. Though most of them reported subjective improvement, objective evidence of this clinically was not forthcoming.

DISCUSSION

Methyl testosterone failed to increase permanently the muscular strength of eleven boys with progressive pseudohypertrophic muscular dystrophy. In two cases muscular weakness progressed more rapidly under treatment. These observations are in general agreement with those of Hoagland, Gilder, and Shank.[6]

Although the metabolic actions of testosterone indicate that it might constitute an ideal approach to the therapy of progressive pseudohypertrophic muscular dystrophy, closer consideration of the factors involved reveal why such therapy has not been of aid.

Histologically, muscle fibers in progressive muscular dystrophy are necrotic and fibrotic, and present no evidence of regeneration.[7] The increases in the mass of skeletal muscle noted after testosterone therapy is due to hypertrophy of the individual fibers. The generation of new muscle fibers has not been observed. Although testosterone might conceivably increase muscle strength through hypertrophy of existing fibers, this was not demonstrated in our study.

Although progressive pseudohypertrophic muscular dystrophy occurs predominantly in male children, and production of testosterone is probably minimal in the prepubertal period, a similar hormonal status exists in young girls who do not develop the disease frequently. That the disease progresses less rapidly in adult males might indicate that a sex hormonal factor influences the progress of the disease. However, enough methyl testosterone was administered in the cases herein reported to evoke secondary sex characteristics without favorable alteration in the progress of the disease.

Increased creatinuria is one of the constant biochemical findings in progressive pseudohypertrophic muscular dystrophy. Testosterone propionate administration decreases creatinuria in normal human beings and in patients with progressive pseudohypertrophic muscular dystrophy, and leads to a positive nitrogen balance.[6] Methyl testosterone decreases total nitrogen excretion, and simultaneously increases the excretion of creatine.[8, 9] This indicates that an increased turnover of creatine[10] occurs in the human being under the influence of methyl testosterone.

The relationship between methyl testosterone and the adrenal cortex may account for the more rapid downhill course of two patients during therapy in the present study, and may possibly constitute a contraindication to the use of methyl testosterone in progressive pseudohypertrophic muscular dystrophy. Urinary 17-ketosteroids, a nonspecific group of steroids, indicate in part adrenocortical activity. The excretion of these steroids decreases when methyl testosterone is administered in large amounts. Methyl testosterone may thus have depressed adrenal cortical function in the two patients who experienced increased weakness. However, there were no other signs or symptoms of adrenal insufficiency in these cases. In addition, the original status was not attained upon cessation of therapy.

In spite of the objective evidence that muscle strength did not increase appreciably, most patients reported that they "felt better." Such a voluntary response did not occur with other forms of therapy. Sufficient amounts of methyl testosterone were given to provide, in addition to secondary sex characteristics, ankle edema (indicative of the Na^+, Cl^-, and water-retaining function of the hormone) and troublesome personality changes.

Thus, one may expect subjective improvement in progressive pseudohypertrophic muscular dystrophy with administration of methyl testosterone with

occasional temporary improvement and some retardation in rate of progress of the disease, but with no permanent benefit.

SUMMARY

1. Eleven young male patients with progressive pseudohypertrophic muscular dystrophy received methyl testosterone in amounts sufficient to promote the appearance of secondary sex characters.

2. Objective evidence (dynamometer studies and throwing ability) failed to reveal sustained clinical improvement in any case.

3. Subjectively most patients felt better.

4. In two cases an exacerbation of symptoms was recorded, and in one case weakness increased when the therapy was suspended.

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THE TREATMENT OF "COLIC" IN INFANCY BY USE OF THE PACIFIER

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THE so-called "colic" baby has been a problem for all pediatricians. He has been treated by changes in formula, by cutting down or enlarging the nipple holes, by changing the type of nipple, by using sedatives and antispasmotics, but the degree of success has not been adequate or satisfactory. In most instances there is a period of time where both parents and infants are extremely unhappy. The parents develop a degree of anxiety which can only be a detriment in the immediate present or to the future attitude and relationship toward the child.

The cause or causes of this crying have also been shrouded in scientific mystery. In some cases the blame has been focused on poor feeding techniques due to inadequate bubbling or improper nipples which either cause difficult sucking or permit the child to suck in and swallow an excessive amount of air. In other cases the blame has been placed on an improper formula for the particular infant or on the possibility of an allergic reaction to the formula, orange juice, or one of the vitamin supplements.

Frequently the distended abdomen, the passage of flatus, and the flexing of the legs have given evidence that abdominal distention is a cause of pain.

It has also been noted that the so-called "colic" baby is in almost every instance a hypertonic infant, differing markedly from the relaxed and placid infant who nurses and sleeps with complete relaxation.

In attempting to study the cause of colic, several questions present themselves.

First, are the crying and irritability always due to abdominal pain?

Second, assuming that the vast majority of "colic" babies are hypertonic infants, will relaxation cause a disappearance of the symptoms?

Third, is there any means of removing the hypertonicity without resorting to constant carrying, continual rockings, or antispasmotic medication?

It has long been recognized that most infants relax completely while being nursed or when sucking their fingers, and that even following the trauma of circumcision, young infants will relax and remain quiet when sucking on a nipple. Many pediatricians have observed the cessation of crying which occurs when a baby's fist is placed in his mouth, or even when the infant is given an empty nipple. Could the pains of colic also be relieved by offering the baby a pacifier?

To answer this question it was decided to treat a series of "colic" babies by the use of the pacifier.

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College, New York.

METHOD OF STUDY

The infants included in this study were all private patients selected over a period of three years. Twenty-eight were chosen because they gave the typical pictures of colic with frequent and daily attacks of restlessness, irritability, and crying. Two other infants have also been included, one the child of a psychiatrist who received the pacifier to prevent thumb-sucking, and the other, an infant placed on the pacifier because of the mother's impression that he constantly desired to suck.

With very few exceptions all babies in this study were on a self-demand or a modified self-demand schedule.

In every instance the pacifier was readily accepted, with the exception of the two cases where the pacifier proved ineffective.

All but three patients were followed from birth and received routine monthly examinations during the first year as well as three routine monthly examinations during the second and third years. Questionnaires on the results of the use of the pacifier were sent to the mothers and filled out when the children were still within their first year or soon enough so that the experience related by each mother was still fresh in her memory. Mothers were questioned at later periods concerning added information such as the length of time the infant continued on the pacifier; if rejected, the manner of rejection of the pacifier; and whether or not the child had later resorted to thumb-sucking.

These reports were studied with particular interest as to (1) the success of the pacifier treatment, (2) the question of whether infants on the pacifier suck in air which, if swallowed, would distend the stomach and abdomen even to a greater degree than usually found in most cases of colic, and (3) the question as to whether the infants resorted to thumb-sucking at any time during the period of observation or subsequently.

It is hoped that a study of other factors to be reported at some later date may throw some light on possible postnatal factors, emotional as well as physical, bearing on hypertonicity.

RESULTS

It is interesting that in every instance, excepting three, the pacifier was successful in relieving the irritability and crying of the infant and in causing a cessation to the symptoms of colic.

The first exception was in the case of an infant who had been relaxed and quiet until 13 weeks of age. At 14 weeks of age the infant started crying frequently for no apparent reason. A pacifier was given the baby, but she would take it from her mouth and play with it as if it were a rattle. The crying ceased spontaneously after several weeks. This case differs from the others in that symptoms of irritability and crying commenced at a much later date than is usually found in typical cases of colic. The spontaneous subsidence of symptoms also would seem to indicate that the difficulty was due to some temporary condition.

In one instance an infant refused the pacifier entirely in spite of attempts of mother and nurse to give it. This child had a history of constant crying and the pacifier was attempted when she was 3 weeks of age. Phenobarbital used as an antispasmotic caused hyperirritability. The irritability and crying subsided spontaneously when the child reached 8 weeks of age.*

In the case of one other infant with a history of considerable crying and "a great deal of gas," the use of the pacifier was discontinued almost immediately since "the whole family were horrified—grandmothers, sisters, cousins, etc."

The time at which the pacifier was offered varied with the period of complaint of the parents, or in certain cases when infants were brought in for the first visit for treatment of the crying and irritability.

The onset of treatment varied as follows:

Age	*No.*
Birth to 4 weeks	16
4 weeks to 8 weeks	7
Over 8 weeks	5

There was no evidence whatever that the pacifier infants swallowed air to such a degree that marked distention would follow. A good many of the infants resorted to the pacifiers almost continuously for a period of time, even sucking the pacifier while sleeping. The sucking on a pacifier seemed to differ considerably from the sucking during nursing. In the use of the pacifier, there was little or no swallowing motion, the activity seemingly being confined to a constant action of the lips.

The pursing of the lips around the pacifier with intermittent slight relaxation and then closure seemed to have an immediate relaxing effect upon the infants. In almost all instances the symptoms of colic disappeared rapidly as soon as the pacifier was taken. One minor difficulty encountered was that of infants losing the pacifier, especially when sleeping. Their cries would bring the parents, who quieted the infants immediately by replacing the pacifiers.

Naturally one wonders whether the giving of a pacifier is establishing a habit which would be difficult to overcome.

The replies from the parents indicate that of the twenty-eight who continued on the pacifier, eighteen had given up the pacifier entirely at the time of this report (Jan. 30, 1950). The ten infants who were still on the pacifier were only using it before sleep.

It is interesting to note that in the process of dropping the pacifier the children seemed to show a diminishing need for it. A number of the mothers stated that the pacifier would be left in the child's bed or playpen where the baby could and would pick it up from time to time and "treating it," as one mother said, "like a man with a cigar—putting it down after a while when he seemed completely satisfied."

Of the eighteen infants who had given up the pacifier entirely at the time of this report, the average age of discontinuance was 13.8 months. The great

*Since the preparation of this paper, we have observed a few babies similar to this case where the pacifier was attempted unsuccessfully for the relief of irritability.

majority of these children rejected the pacifier spontaneously and in some instances even suddenly as if they had no further desire or need for it. In three instances the pacifier was discontinued by the parent. In one instance it was discontinued at 12 months of age, in another at 24 months of age, and in the third at 27 months of age. The mother who withdrew the pacifier when her child was 12 months of age had moved away from New York and was acting on her own volition. According to her report, the infant seemed very unhappy and cried frequently for several weeks, but finally readjusted. In the second case, the pacifier was discontinued at 24 months of age without any difficulty. The mother of the 27-month-old child compensated by teaching her child to chew gum. In none of these three cases did the child resort to thumb-sucking after the pacifier was denied.

It is significant that of the twenty-five pacifier infants who were 18 months of age or older on Jan. 30, 1950, only two had resorted to thumb-sucking and these only when going to sleep. It might be noted that the two thumb-sucking infants gave up the pacifier at a comparatively early age—one at 5 months and one at 10 months.

TABLE I. CHILDREN STILL ON PACIFIER OR THUMB SUCKING AT VARIOUS AGE LEVELS

AGE LEVEL	14 MO. OR OLDER (WHOLE GROUP)	18 MO. OR OLDER	24 MO. OR OLDER
Pacifier infants	28	25	19
Still on pacifier Jan. 30, 1950*	10	8	4
Thumb-suckers*	2	2	1

*Only before going to sleep.

A control study of the comparative degree of thumb-sucking of "colic" babies treated by pacifier and by other methods will be dealt with in a subsequent paper.

DISCUSSION

It is generally accepted today on the basis of experimental studies that an infant not only has a sucking reflex but, more than that, a sucking urge—a definite need for oral satisfaction. This need is entirely separate from the necessity of sucking as an adjunct to eating. This fact was pointed out originally by Freud, who placed emphasis on the importance of the oral zone, not only in the desire for feeding but in the desire for sucking as well.

That oral satisfaction seemed to give to the infants a sense of relaxation was recognized centuries ago. Bragman[1] demonstrated that artists used thumb-sucking "as subjects for pictures expressing peace and sublime tranquility." The degree of relaxation afforded by sucking is easily evident to the pediatrician as well as to all who have observed the developing infant. Some pediatricians even have made it a practice to place the fist of a crying infant at his mouth so that the child will start sucking and be relaxed while they examine the heart and the lungs.

It has also been pointed out how children, when deprived of oral satisfaction, resorted to thumb-sucking as a substitute. Some of the early work

on this subject was performed by D. M. Levy.[2, 3] A more recent study by Klackenberg[4] reported the results of thirty-two infants who had been placed on pacifiers (dummy teats). Among those who had used the teat for over three months (twenty-eight cases the greater part of the first year of life), there were no thumb-suckers. In two of the remaining infants who used the teat for a short time only, the thumb-sucking had commenced in association with giving up the teat, and in the last two cases the habit had begun several months later.

The results of our studies on the use of the pacifier in the relief of infantile colic seem to indicate that the crying of the infants may be due either directly or indirectly to an unsatisfied need for adequate oral gratification. The relief from colic which in the great majority of cases quickly followed the use of the pacifier leads one to surmise that the crying was due to one or both of two causes. Either the infant was unhappy because of an unfulfilled desire to suck, or the tension due to this lack of oral satisfaction causes an otherwise passive infant to become tense, which, in turn, might result in intestinal spasm with distention and its accompanying pain.

The fact that certain crying infants do not respond to the pacifier by relaxation would lead to the conclusion that their difficulty was probably due to an etiological factor unrelated to the need for sucking. However the great proportion of our cases that responded to the use of the pacifier focuses attention on oral deprivation as a primary factor in the etiology of colic.

This need for oral satisfaction definitely diminishes as the infant grows older; the average age of discontinuance of the use of the pacifier was 13.8 months. In only two of the twenty-eight cases was there any thumb-sucking following the discontinuance of the use of the pacifier and in these two cases only before sleep. This coincides with the findings of Levy and Klackenberg.

SUMMARY

1. The "colic" baby has been a problem for all pediatricians.

2. The various theories as to the etiology of colic are discussed.

3. Twenty-eight infants with histories typical of colic were placed on pacifiers.

4. In every instance except two the pacifier was readily accepted.

5. With the exception of three infants, the pacifier was successful in relieving the irritability and crying of the infant and in causing a cessation of the symptoms of colic.

6. The favorable results of our studies on the use of the pacifier in the relief of infantile colic seem to indicate that the crying of the infants may be due either to an unsatisfied need for adequate oral gratification, or from abdominal pain caused by the spasm of intestinal muscles resulting from the general hypertonicity of the infant.

7. The use of the pacifier does not form a habit, the children discarding it spontaneously at an average age of 13.8 months.

8. In only two of the twenty-eight cases did infants resort to thumb-sucking during or after discontinuing the pacifier, and these two only while going to sleep after the pacifier had been discarded.

9. The fact that certain crying infants do not respond to the pacifier by relaxation would lead to the conclusion that their difficulty was probably due to an etiological factor unrelated to the need for sucking.

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ACUTE THALLOTOXICOSIS: REPORT OF TWO CASES TREATED WITH BAL

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THALLIUM is a potent insecticide and vermicide, frequently disguised in pleasant-tasting media. Such disguise may fascinate toddlers and small children if left within their range of curiosity.

Two cases of thallium intoxication were observed simultaneously from "Quick Kill,"* a crushed vanilla wafer insecticide containing thallium sulfate 2.25 per cent. Both children, playmates, sampled repeatedly over several weeks the treasured cookie crumbs in the one ounce jars.

One of the two patients developed complete muscular weakness, incoordination, loss of speech, and extreme polyneuritis in addition to the complete alopecia. He was semicomatose for four days before BAL was administered. The other child had transient, though definite, signs of cerebral and cerebellar irritation.

Mezzei and Schaposnik[1] reported the use of BAL in a suicidal attempt with thallium. They reviewed the pharmacology and toxicology of BAL and gave a suggested dosage schedule based on other heavy metals. We were unable to find other reference to use of BAL in thallotoxicosis in the medical literature.

REPORT OF CASES

CASE 1.—D. McK., a 4-year-old white male, was first seen because of an acute follicular pharyngotonsillitis. After having apparently responded to conventional dosages of intramuscular penicillin, he returned one week later with fever, cough, and many fine râles in both lung fields. Immediately prior to this visit he had developed drooping eyelids, and complained bitterly of severe arm and leg pains. At this time there was bilateral ptosis and a moderate degree of lethargy. Aureomycin hydrochloride in doses of 30 mg. per kilogram of body weight per twenty-four hours was begun. On the third day of this therapy the parents reported progression of the ptosis, increased lethargy, "mumble jumble" speech, stumbling and falling, and moderate tremors of both hands. It was noticed that some of his hair was "falling out." There was extreme irritability, and the examiner was impressed with the picture of abject misery.

Further questioning revealed that prior to the onset of the present illness he had played for several weeks in a lead vat filled with "BB" shot; on several occasions his hands were coated black. During this period he had also accompanied his father repeatedly to new house construction where he played around fresh painting (lead paint) and plumbing work using soft lead joints. The patient was hospitalized with provisional diagnosis of heavy metal poisoning, probably acute lead poisoning, but the strong possibility of thallium poisoning was considered.

*Quick Kill Exterminating Company, Woodsboro, Texas.

While in the hospital evidence of cerebral and cerebellar irritation progressed as did the alopecia, to become complete. Gross tremors of the hands were outstanding, and there was bilateral wrist and ankle drop (Fig. 1). A semistuporous state prevailed for ten days after admission. The funduscopic examination was normal on each of three occasions. The consulting ophthalmologist discovered no central scotoma or other visual abnormalities. Otherwise the physical examination, except as noted, was negative. Laboratory studies were not helpful in a positive sense. The initial hemogram and urinalysis were negative; no basophilic stippling was observed. Examination of the spinal fluid revealed no cells, sugar 72.5 mg. per cent, chlorides 730 mg. per cent, and protein of 30 mg. per cent. The fluid did not flow with increased pressure although manometric readings were not taken. Spinal fluid examinations repeated seven days later were again noncontributory; hemograms repeated at three-day intervals remained normal.

Fig. 1 (Case 1).—Showing bilateral ptosis and wrist drop with masked facies.

Roentgenograms of the long bones failed to reveal lead lines; x-rays of the heart and lungs revealed no abnormality. The parents repeatedly denied any possibility of ingestion of, or contact with, preparations which might contain mercury or thallium; thallotoxicosis was the diagnosis to be disproved.

British anti-lewisite (BAL, 2,3-Dimercaptopropanol) was begun on the fourth hospital day when cerebral irritation was most pronounced; prognosis, at this point, seemed hopeless. The initial dosage of 5 mg. per kilogram of body weight per twenty-four hours in divided doses was given as suggested by Bivings and Lewis[2] for mercury poisoning as no reference to thallium intoxication was available at this time. The therapy was continued at this level every four hours for three days without noticeable improvement. No flushing or hypertension developed to suggest toxicity or therapeutic effectiveness. Immediately following cessation of treatment he was as ataxic and lethargic as before. However, forty-eight hours later the ataxia diminished sufficiently to enable him to partially feed and clothe himself, and his speech began to clear. Fourteen days following treatment the wrist and ankle drop, ptosis, and tremors were no longer present. He walked unassisted and was discharged. One month later only alopecia remained as evidence of his intoxication; many fine new hairs were appearing.

CASE 2.—S. S., a 4-year-old white female and playmate of the preceding patient, was brought to our attention because of complete loss of hair of three weeks' duration, and because we were treating her playmate (Case 1). The girl had been seen during the early febrile course by the family physician who referred her to a dermatologist when the alopecia developed. The latter physician diagnosed the case as "total alopecia due to some toxemia" and sent her back to her home town on topical treatment.

Her mother stated that about one week prior to the beginning of the alopecia the girl complained of severe headaches, was very fussy, irritable and had a temperature of 101° F. These complaints subsided prior to the loss of hair; she had no evidence of polyneuritis, ataxia, tremors, slurred speech, or stupor, but had had some transient mild personality changes during the time when the headache was severe.

Close questioning revealed these two children to have played together during the preceding four weeks, including the lead contacts. Three days following her hospitalization she volunteered to her mother that she and her playmate had been eating some crushed cookies in a jar in a neighbor's yard. Upon investigating, her mother found a large open carton containing 100 jars of "Quick-Kill" in the yard where they had been for several months. It was then determined that the girl had eaten only a small amount of the poison-containing crumbs but that the boy had eaten the contents of almost four jars over an estimated period of ten days.

Physical examination revealed the total alopecia as the only detectable abnormality in an otherwise healthy 4-year-old female.

The hemogram and urinalysis were negative; roentgenograms of chest and long bones were normal. A spinal fluid examination was not performed.

BAL was administered for three days, 5 mg. per kilogram of body weight per twenty-four hours, then discontinued because of nausea and vomiting; no flushing or hypertension appeared. With symptomatic treatment, improvement was steady, and she was discharged ten days after admission. One month later many fine new hairs were visible, although the alopecia was still prominent.

COMMENT

The use of BAL in the first instance may have been responsible for the child's survival as he was considered moribund at the time of its institution. We are not able to state conclusively the role BAL played; however, in view of the known effectiveness with some heavy metals it was deemed worthy of trial. Further opportunity to study the usefulness of British anti-lewisite in the management of acute thallotoxicosis should be undertaken as new cases present themselves to enable formulation of accurate dosage schedules as well as its true value.

The use of such an acute intoxicant in common household poisons points up the necessity for closer control and more adequate warnings to parents. Two such instances present clearly the dictum that when poisoning is suspected one should not cease questioning until the toxic agent is revealed.

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PRENASAL AND PREORAL AUSCULTATION

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THE techniques of physical diagnosis have been long established in medical customs and need seldom now be the subject for communications in our journals. However, most of the teaching of medical students in the basic principles of physical examination is on adults where cooperation is expected. With only minor variations these same techniques are taught as the basis for examination of infants where lack of cooperation, crying, or actual resistance is frequently encountered.

This communication is to advocate the advantages of preoral or prenasal auscultation in the physical examination of infants and children as a means of evaluating respiratory function without disturbing the quiet or sleeping patient. By the phrase, prenasal or preoral auscultation, we mean to identify the technique of listening with the bowl of the stethoscope held over, or in front of, the patient's nose or mouth where most of the sounds of respiration produced within the body can be readily heard, collected, as it were, and concentrated at this one point with little loss.

It is rightly taught that simple inspection of the thorax should precede any other part of the examination; but simple observation of the clothed infant may be unprofitable, while often the process of undressing the child so disturbs him that opportunity for subsequent satisfactory observation of respiration is prevented. Although important information can be obtained by observation and auscultation of the chest of a struggling or crying child, certainly opportunity for examination only under those circumstances is greatly handicapping. Very frequently the opportunity exists to approach first a quiet or sleeping infant to observe whether any form of dyspnea, hyperpnea, or obstructed breathing exists, but any attempt at removing the clothing or even touching the child arouses it or causes it to become resistant, and ends the possibility for best evaluation of its basic respiratory condition.

It is my custom in teaching and practice, first to listen over the nose or mouth of the undisturbed infant before any attempt at undressing him or a systematic survey of the various areas of the chest is made. By this prenasal auscultation, a great deal of information can be obtained with great ease, often information that cannot be acquired by any other method. The technique is the essence of simplicity. Even to the inexperienced physician the sounds of the inspired and expired air heard over the nose or mouth, depending upon how the child is breathing, can convey important information, and with only a little experience one develops great accuracy in interpretation of what one hears.

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The stethoscope is held usually one-half to one inch from the nose in the path of the respired air current. The small infant, if awake, usually detects the stethoscope in front of his mouth with only mild interest or apathy, although, of course, the older child may resent even the presence of the physician at the bedside. As with the customary use of the stethoscope, the physician becomes familiar with the use of one instrument and develops his own standards of quality of sound. The actual sounds heard are quite similar to those made familiar by traditional auscultation and have, of course, similar significance. Even a very faint inspiration or expiration can be clearly heard, and the quantity of air moved can be soon estimated after a little experience with one's stethoscope. More accurately than by traditional auscultation, it can be determined whether or not hyperpnea exists and the blood CO_2 level can be estimated with reasonable approximation. Reduction of CO_2 levels below 30 vol. per cent is usually readily detectable. Evaluation of the sum of tidal air and of pulmonary ventilation can be more accurately made by prenasal auscultation than by listening to one area of the chest or by attempts to summarize impressions gained by listening at numerous points.

The presence of even slight obstruction is made very evident by the quality of sounds heard, and it becomes immediately obvious whether the obstruction is in inspiration or expiration. Bilateral multiple obstruction such as in "capillary bronchitis" or, of course, asthma, is strikingly evident although a localized unilateral obstruction that is complete, or obstructive emphysema, is not apparent.

Irregularities of breathing which would disappear immediately if the child were disturbed are obvious and under conditions of gentle respiration are much more clearly detected by prenasal auscultation than by inspection.

Fairly fine râles can be heard and easily distinguished from more coarse ones, and their probable origin (i.e., medium- or small-sized bronchi) can be determined with accuracy although the location within any particular part of a lobe is not possible. Tracheal or bronchial ronchi are, of course, often heard without the aid of a stethoscope.

The great respiratory difficulty of an infant, especially a premature one, when nasal obstruction exists, should be well known but it is often unrecognized. In a recent case of an infant with obvious and severe obstructive dyspnea, several competent physicians after careful chest examination were confused and puzzled until the fact of nasal obstruction was made quickly evident by first prenasal and then preoral auscultation.

In rare circumstances, such as the incarceration of a patient in a Drinker respirator, the technique of prenasal auscultation is invaluable. In an oxygen tent where examination of the lungs can be carried out with only considerable and sometimes serious disturbance of the patient and with interruption of oxygen therapy, this technique is of very great value. In the child whose diagnosis is already established, such as one with pneumonia or "croup," or in cardiac failure, often only preoral auscultation is necessary for frequent follow-up observation of progress, made much more accurately than by simple inspection.

With the availability of many modern physical diagnostic devices, such as fluoroscopy or blood oximetry, we are likely to underemphasize to the student that often much more can be learned by simpler techniques. For instance, the determination of hemoglobin-oxygen saturation by the most perfectly adjusted ear oximeter does not convey to us the magnitude of the pulmonary ventilation that may be present or the amount of effort that the patient needs to exert to produce this degree of oxygen saturation. Although there exists no way yet of evaluating respiratory effort quantitatively, an excellent estimation can be made by a physician by simple observation supplemented by a little practice with the stethoscope. The quick determination by prenasal auscultation that a usual or increased pulmonary ventilation is being maintained in a patient with definite cyanosis readily indicates the probable futility of oxygen therapy and directs the physician to make further diagnostic efforts.

SUMMARY

It is recommended that as a routine in examination of infants and small children, the technique of prenasal and preoral auscultation be used before the patient is touched or before his clothing is removed for traditional routines of examination.

AMMONIA DERMATITIS: TREATMENT WITH DIAPARENE CHLORIDE OINTMENT*

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AMMONIA dermatitis, first described by Jacquet,[1] in 1886, as diaper dermatitis, is also known as napkin erythema, erythema gluteale, or diaper rash. Although the apparent cause of this condition appeared to be the wet diaper, impregnated with urine, the actual cause is contact with ammonia. Such dermatitis may also be caused by contact with other articles soiled with urine, such as underclothes, bed sheets, mattresses, or surgical dressings. As the offending substance is ammonia, it is well to use the term ammonia dermatitis.

In 1921, Cooke[2] proved conclusively that the ammonia was the result of the presence of fecal bacteria which liberate ammonia from the urea in the urine, due to the following well-known reaction:

$$CO(NH_2)_2 + 2\ H_2O = (NH_4)_2\ CO_3 = 2\ NH_3 + H_2O + CO_2$$

In all cases examined he was able to isolate a urea-splitting organism from the feces in pure culture. This organism, which he named the *Bacterium ammoniagenes*, is an aerobic, nonmotile, gram-positive bacillus, which does not ferment ordinary sugars or form spores. Morphologically, the organism is a rather short, straight rod with well-rounded ends, measuring 0.8×1.4 microns. Cultures grow well in room and incubator temperatures. When grown in media containing urea, the alkalinity reaches a pH of 9.3, at which point growth is considerably inhibited. This bacillus is present in the stools under normal conditions, but when the intestinal contents are of a low acidity, the number of such organisms is greatly increased and consequently the diaper region becomes infected from the feces. Other organisms, such as the *Staphylococcus albus* and *aureus*, have a similar effect on urea. The bacteria grow in urine and split the urea, liberating ammonia which causes the dermatitis.

TREATMENT

Since the establishment or demonstration that the cause of ammonia dermatitis is the *B. ammoniagenes* which acts on the urine to produce ammonia, research has been directed toward finding a nonvolatile antiseptic for diaper impregnation. A 1:4,000 solution of mercury bichloride has been shown to be effective as a diaper rinse. Mercury bichloride, however, is a dangerous poison, and even when applied externally, it may cause contact and eczematous dermatitides of the hands. It is also dangerous to have it in the home, as children may swallow the tablets. The concentration varies and the tablets are

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*Diaparene chloride ointment used in this project was supplied by the Homemakers' Products Corporation, New York, N. Y.

not easily soluble. Boric acid, in a 1:20 dilution has also been recommended for a diaper rinse, but this drug is now reported as having no antiseptic value (Gordon,[3] Goodman,[4] Sollmann[5]), is not readily soluble and is dangerous in the household (Bazin,[6] Birch,[7] McNally,[8] Pfeiffer,[9] Watson,[10] Ross,[11] and Abramson.[12]

Benson and collaborators[13, 14] made studies on Diaparene Chloride, which proved to be a most effective bactericide against *B. ammoniagenes.* They treated 500 patients with ammonia dermatitis with Diaparene chloride-impregnated diapers. Within one week 436 of the patients were cured. This drug is a quaternary ammonium compound; namely, para di-isobutyl-cresoxy-ethoxy-ethyl di-methyl benzyl ammonium chloride monohydrate. It was also found to be highly effective against the streptococcus and the *Staph. aureus* by Klarmann and Wright.[15] Quisno[16] used a neutralizing medium for evaluating the germicidal potency of the quarternary ammonium salts. Diaparene chloride has also yielded excellent results in patients with excoriations due to urinary incontinence in neurologic and urologic disease and surgical operations on the urinary tract (Nagamatsu and collaborators[17]).

RESULTS WITH DIAPARENE CHLORIDE OINTMENT

The purpose of this study was to determine whether Diaparene chloride in a suitable ointment is also efficacious in the treatment of ammonia dermatitis.[18]

Bacteriologic studies by Fanchon and Huyck[19] show the drug to be effective in a modified hydrophilic petrolatum base. Diaparene chloride ointment acts specifically upon the urea-splitting organisms which originate in the excreta and are found on the skin. Diaparene chloride ointment has been tested by the wet and dry filter paper and agar cup-plate methods against *B. ammoniagenes* and *Staph. aureus* and has been found to be bactericidal. The phenol coefficient method should not be used according to Klarmann and Wright,[15] because it gives erroneously high value for the disinfecting potency of these salts.

A series of 107 infants with ammonia dermatitis were treated with Diaparene chloride ointment by application at the time of each diaper change. The subjects were not chosen but treated consecutively. There were about an equal number of male and female infants whose ages ranged from 5 days to 2½ years. As a large number of the patients were hospitalized, an excellent opportunity was afforded for careful evaluation. All the children were artificially fed except five. The time for cure ranged from one day to three weeks. In eight cases the dermatitis did not clear up after three weeks; three of the failures may have been due to an atopic infantile eczematoid dermatitis with secondary infection. When this condition was improved, the ammonia dermatitis was cured.

PATCH TEST WITH DIAPARENE CHLORIDE OINTMENT

To ascertain whether or not the ointment is a primary irritant or a secondary sensitizer, fifty infants and children were patch-tested. The patch

test was applied in the usual manner on the back or on the arm with a half-inch square gauze covered with waxed paper and held in place by adhesive tape. In ten subjects the patch test was removed after twenty-four hours, in twenty, after forty-eight hours, and in the remaining ten, after seventy-two hours. There were no reactions to the ointment. There were, however, numerous reactions to the adhesive tape. Several brands of adhesive were tried including a nonallergic type which did not alter the sensitivity to the adhesive. The patch tests are in agreement with similar tests done by Dr. Reuel A. Benson.[20] Therefore, it would appear that the ointment has no sensitizing qualities.

SUMMARY AND CONCLUSIONS

1. Excellent results are described in a series of 107 cases following application of Diaparene chloride ointment with each change of diapers, treated from one day to three weeks. Eight were unimproved, three of whom had an accompanying infantile eczematoid dermatitis.

2. Patch tests of fifty subjects yielded no evidence of sensitivity to the ointment.

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Case Reports

FATAL PAROXYSMAL TACHYCARDIA IN A NEWBORN INFANT WITH THE WOLFF-PARKINSON-WHITE SYNDROME

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PAROXYSMAL tachycardia has been reported with increasing frequency in the very young. Hubbard[1] described nine cases of paroxysmal tachycardia in infants under one year of age; six of these were encountered in a period of one year. Cardiac arrythmia in infants may be more frequent than the literature indicates, and many unexplained complications including sudden death may be on the basis of unrecognized paroxysmal tachycardia.

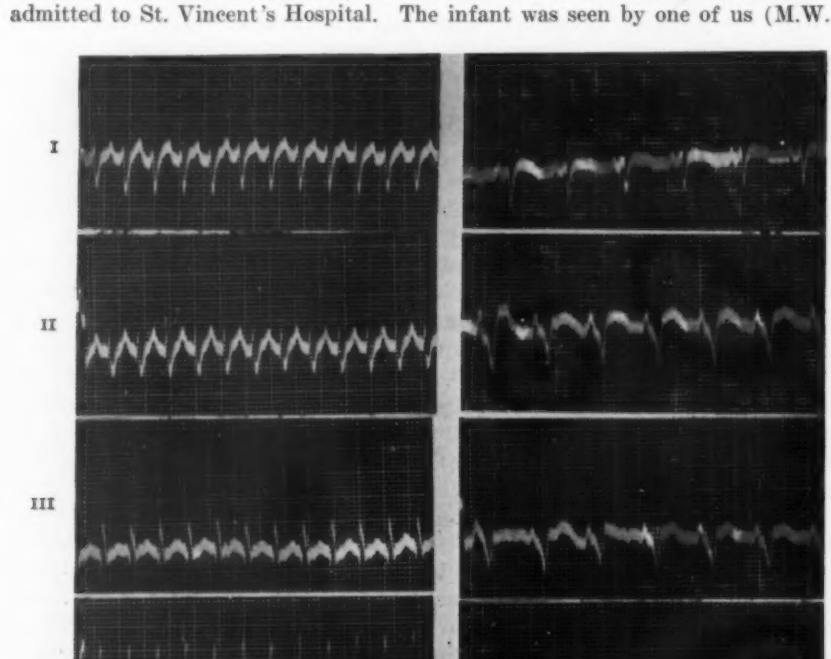
Unless frequent electrocardiograms are taken, both during and after episodes of tachycardia, rapid heart action in the young may be misinterpreted and the true nature of the condition missed. One of us recently encountered a fatal paroxysmal tachycardia with a ventricular rate of 365 per minute in a 5-week-old infant.[2] The child was at first treated for bronchopneumonia, and the correct diagnosis was not established until late in the illness. In this present report we wish to describe another fatal supraventricular tachycardia in an infant with a ventricular rate of 300 per minute. The infant was subject to frequent attacks of paroxysmal tachycardia. Many electrocardiograms were taken, both during and after the tachycardia. Between attacks the infant demonstrated a distinctive type of electrocardiogram characterized by a short P-R interval and an abnormal QRS complex (Fig. 2). It is now well established that patients with this type of electrocardiogram, first described as a syndrome in 1930 by Wolff, Parkinson, and White,[3] are notoriously prone to develop paroxysmal tachycardia. Contrary to early reports the syndrome is far from benign as emphasized by the fatal outcome in our case. The Wolff-Parkinson-White syndrome is common in the young, but to our knowledge this is the first documented case reported so early in the newborn infant.

CASE REPORT

S. G., a white male, was born at St. Vincent's Hospital, Staten Island, N. Y., on Jan. 22, 1950. Labor and delivery were uneventful; no anesthesia was used. There was one other sibling, aged 16 months, who was considered allergic to oranges and chocolate. During pregnancy the mother's health was said to be excellent. At birth the child weighed 7 pounds, 13 ounces. The infant was breast fed for the first seven days, after which a cow's milk formula was prescribed. Circumcision was performed on the seventh day, and on that day inconsequential, brief periods of cyanosis were observed. The baby, however, was carefully examined and was found to be in good health, and discharged from the hospital on the eighth day, weighing 7 pounds, 10½ ounces.

On the second day, following discharge, at the age of 10 days, the mother observed that the infant was breathing rapidly, seemed unusually restless, and intermittently "changed color." The formula was refused. The family physician was notified, and on examination the child was found to be normal except

for extreme irritability. The restlessness, tachypnea, and intermittent cyanosis were attributed to the baby's crying. No medication was prescribed. The symptoms, however, progressed and at 3 A.M. the next morning the child was admitted to St. Vincent's Hospital. The infant was seen by one of us (M.W.)



A. *B.*

Fig. 1.—The electrocardiogram shown in *A* was taken during an episode of supraventricular tachycardia. The electrocardiogram shown in *B* was taken the same day immediately after the cessation of the tachycardia. Note the short P-R interval and abnormal QRS complexes in *B*.

an hour later. By this time the child was in an oxygen tent. There was moderate cyanosis of the lips, ears, fingers, and toes. The respirations were labored and extremely rapid, averaging 100 per minute. The general nutrition and development were normal. The rectal temperature was 96.2° F. On physical examination the striking finding was an extremely rapid heart rate, too rapid to be counted accurately, but estimated to be over 250 per minute. The heart sounds were regular and no murmurs were noted. The lungs were normal to auscultation and there was no abnormal dullness to percussion. The abdomen was distended and tympanitic. The splenic edge was palpable at the costal margin; the liver was enlarged to the level of the umbilicus. The naval was healed and dry. The circumcised edges of the foreskin showed evidence of healing. There were no rashes, edema, or congenital stigmas.

Laboratory studies disclosed a red cell count of 3.5 million per cubic millimeter; hemoglobin 11 Gm. per 100 c.c.; white blood count 16,400 with 73 per cent polymorphonuclear cells and 27 per cent lymphocytes; a normal urinalysis except for a trace of albumin; normal values for blood nonprotein nitrogen, blood urea, and blood sugar determinations; and the blood Mazzini test for syphilis was negative. An electrocardiogram (Fig. 1) taken shortly after admission disclosed a supraventricular tachycardia with a ventricular rate of 300 per minute. A roentgenogram of the chest (Fig. 3) disclosed congestion at both hilar regions.

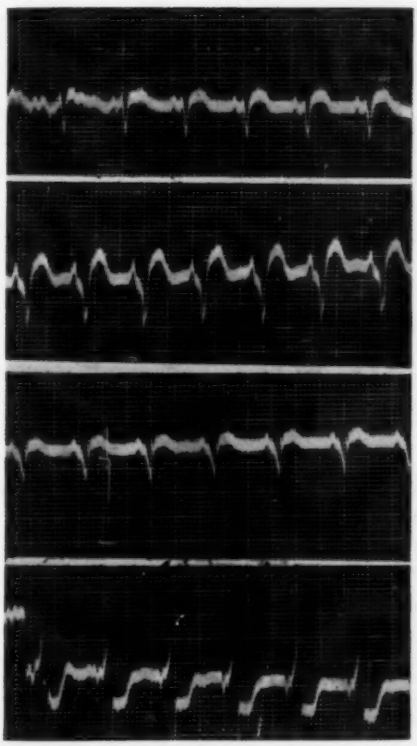


Fig. 2.—The electrocardiogram was taken three weeks prior to death. At this time the infant was symptom free and under digitalis medication. Compare with Fig. 1*B*.

When the diagnosis of paroxysmal tachycardia was established with certainty, attempts were made to abolish the abnormal rhythm by pressure on the carotid sinus. Carotid sinus pressure was ineffective and it was decided to resort to pharmacologic techniques. A summary of the drugs used is shown in Table I. Digitalis was first prescribed. Digoxin, 0.1 mg., was administered intravenously, and the dose was repeated by the same route two and one-half hours later. Three and one-half hours after the second dose another electrocardiogram was taken; the tachycardia remained unchanged. By this time the respirations appeared more labored and the cyanosis more intense. Acetyl-

beta-methylcholine chloride (Mecholyl-Merck) was next cautiously administered. The first dose was given subcutaneously in the amount of 0.5 mg., followed by a similar dose seven minutes later, after which a third dose five minutes later of 1.0 mg. was given. The total dose of Mecholyl administered by the subcutaneous route was 2 mg. No therapeutic response was observed; in fact, the infant's condition rapidly deteriorated and now appeared moribund. In desperation, with 1 mg. of Mecholyl, dissolved in physiologic saline, remaining in the hypodermic syringe, it was decided to inject this drug intravenously. Accordingly, the drug was injected slowly into one of the antecubital veins, and

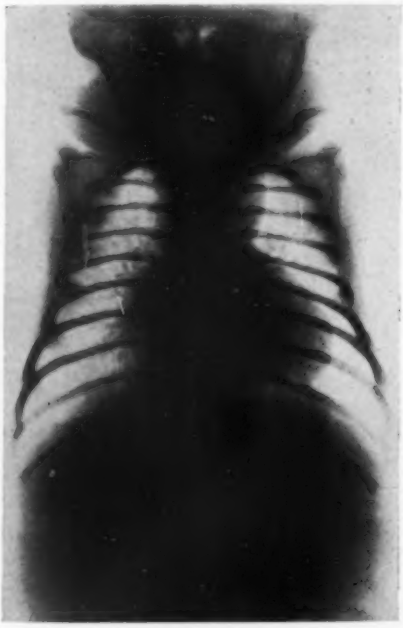


Fig. 3.—Roentgenogram of the chest taken during an attack of paroxysmal tachycardia.

with the stethoscope applied constantly over the apical region of the heart during the injection, the heart sounds suddenly became inaudible after 0.5 mg. of Mecholyl was administered. Therapy was immediately discontinued and in a few moments the heart rate was distinct and regular at 150 per minute. Cyanosis disappeared and the respirations dramatically improved. Atropine sulfate was held in readiness but not used. Two hours following the intravenous injection of Mecholyl, the infant was again cyanotic, but this time the heart rate was 154 per minute and regular. Because of some restlessness, 0.5 gr. of sodium luminal was prescribed parenterally. The following day a slight icterus became visible and a grade I systolic murmur was heard in the fourth intercostal space just to the left of the sternum. The general condition of the baby, however, was good; the heart rate varied from 128 to 144 per minute. On the seventh hospital day the child suddenly became cyanotic again and the respira-

TABLE I. SUMMARY OF FIRST HOSPITAL ADMISSION INDICATING FREQUENCY OF TACHYCARDIA, DRUG USED, AND RESPONSE OBTAINED

DAY OF HOSPITAL	HEART RATE	DRUG	EFFECT
1st 4:30 A.M.	280-300		
9:30 A.M.	300	0.1 mg. digoxin	None
4:30 P.M.	300	0.1 mg. digoxin (intravenous)	None
8:35 P.M.	250	Mecholyl (subcutaneous)	None
8:42 P.M.	250	Mecholyl (intravenous)	Relief
8:47 P.M.	250		
8:48 P.M.	150		
2nd	130-150	None	
3rd to 6th	120-150	None	
7th	250	1 mg. Mecholyl (subcutaneous)	Relief
8th to 10th	120-150	None	
11th	120-150	Tincture of digitalis started	None
12th	250	0.1 mg. digoxin, repeated several hours later	Relief
13th to 16th	120-140	Tincture of digitalis cont'd	
17th	250	None	Spontaneous relief
18th	130	None	
19th	250	None	Spontaneous relief
20th to 25th	108-120	Tincture of digitalis	

tions rapid and labored. On auscultation the heart rate was extremely rapid. An electrocardiogram taken at this time disclosed a supraventricular tachycardia with a rate of 250 per minute. One milligram of Mecholyl was administered subcutaneously and within a few minutes the heart rate dropped to 130 per minute. The baby continued to do well, and on the eleventh hospital day tincture of digitalis was prescribed, 3 drops three times a day for the first day, followed by a dose of 2 drops daily. On the twelfth hospital day a recurrence of the tachycardia occurred. Digoxin was given intravenously in divided doses of 0.1 mg. each. The heart rate decreased to 140 per minute twenty-five minutes after the second dose of digoxin. On the fourteenth hospital day digitalis was increased to 1 drop three times a day. An episode of tachycardia was observed on the seventeenth hospital day, and while preparations were being made to inject digoxin, the tachycardia spontaneously subsided to 130 per minute. On the nineteenth hospital day a transient tachycardia lasting less than ten minutes was detected. The baby, however, continued to do well and was discharged on the twenty-fourth hospital day with a maintenance dose of 1 drop of tincture of digitalis twice a day. At the time of discharge the infant weighed 8 pounds, 7 ounces.

The infant was not seen by us again after this last admission. One week after discharge from the hospital, the infant developed a bout of vomiting, loose bowel movements, and cyanosis. A diagnosis of acute catarrhal pharyngitis was entertained and the baby was admitted to the hospital where he remained for seven days. During this hospital admission, the heart was carefully examined and no tachycardia was noted. No murmurs were heart. Penicillin was prescribed and the child promptly returned to a normal status. No electrocardiograms were taken during this admission.

On March 15, 1950, while at home, the infant suddenly developed intermittent cyanosis, labored breathing, and abdominal distention, and on that day was admitted to St. Vincent's Hospital for the final admission. There was a history of recent exposure to measles, and 2 c.c. of immune globulin was admin-

istered intramuscularly. On physical examination there was again evidence of extreme tachycardia, averaging 300 per minute. The infant at this time demonstrated obvious signs of advanced congestive circulatory failure. The liver edge was palpable below the umbilicus, and there were many moist râles heard throughout both lungs. The abdomen was distended; cyanosis was intense. The respiratory rate was 120 per minute. Mecholyl, 1 mg., was administered subcutaneously, and the heart rate promptly dropped to 140 per minute. Five drops of tincture of digitalis and 0.5 c.c. of Mercuhydrin were administered to combat the congestive circulatory failure. The infant, nevertheless, continued to do poorly. He ran a febrile course, the temperature averaging 103° F. Penicillin, streptomycin, aureomycin, and oxygen were administered. On the third hospital day at 8:30 P.M. the heart rate jumped to 300 per minute, and Mecholyl, 1 mg., administered subcutaneously was again effective in abolishing the extreme tachycardia. However, at 10 P.M. congestive circulatory failure was now profound with the respirations rising to 130 per minute. Coramine, 1 c.c., and atropine sulfate, 1/500 gr., were administered without any apparent response. At 10:30 P.M. the child suddenly expired. No autopsy was obtained.

DISCUSSION

A voluminous and conflicting literature has accumulated regarding the mechanism responsible for the distinctive type of electrocardiogram first described by Wilson,[4] and later noted in a group of patients by Wolff, Parkinson, and White.[3] It is generally assumed that the abnormal electrocardiogram results from an anomalous condition operating through an accessory conducting pathway connecting the auricle and ventricle.[5, 6] This results in early and abnormal activation of ventricular depolarization. The fact that most instances of this syndrome have been reported in the early decades of life, in our case seven days after birth, suggests a congenital defect of the conduction mechanism. This anatomic explanation is not completely satisfactory, however, and attempts have been made to explain this syndrome on a physiologic basis.[7]

In the Wolff-Parkinson-White syndrome the electrocardiogram between attacks of tachycardia is characterized by two features: a short P-R interval and an abnormal QRS complex. The P-R interval is less than 0.10 second in most cases, and the QRS complex usually demonstrates a large deflection that is slurred and occasionally notched. In the majority of instances, the QRS interval measures from 0.11 to 0.14 second. As previously stated, patients with this type of electrocardiogram are subject to paroxysmal tachycardia, occurring in one series[8] as high as 70 per cent of the patients studied. According to Wolff[9] in more than one-half of the cases a normal ventricular complex will be demonstrated, either spontaneously or as a result of exercise, following the administration of a wide variety of drugs, carotid sinus stimulation, performance of the Valsalva experiment, and during paroxysmal tachycardia.

The prognosis in the Wolff-Parkinson-White syndrome is generally considered benign and depends on the frequency and duration of the paroxysmal tachycardia. Nevertheless, there have been an increasing number of deaths reported in this syndrome. Up to the present time[10, 11] there have been eight reported fatalities in patients with the Wolff-Parkinson-White syndrome in whom

it was considered that the syndrome was responsible for death. The death in our patient is the ninth instance attributed to this syndrome, and the second to occur at an extremely early age. Kimball and Burch,[11] in a review of the subject on the prognosis of the Wolff-Parkinson-White syndrome, also described a sudden death in an infant 8 months of age with a history of paroxysmal tachycardia since the age of 2 weeks.

In the differential diagnosis of tachycardias in infants the Wolff-Parkinson-White syndrome should be kept in mind. This syndrome may be more frequent in infants than the literature indicates, and perhaps more vulnerable. Paroxysmal tachycardia in infancy can easily escape detection. Paroxysmal tachycardia may be brief, and between attacks the child may appear perfectly normal. In the very young the heart rate is extremely labile. Normally, the heart rate of a newborn infant may rise to over 130 per minute. Heart rates over 200 per minute are not always easy to count, especially in restless infants with associated respiratory difficulties. Congestion of the lungs resulting from tachycardia may be interpreted erroneously as bronchopneumonia if there is an associated temperature, and an elevated blood count. Vomiting and other gastrointestinal disturbances are often present in paroxysmal tachycardia, and may be attributed to pyloric spasm. Convulsions, resulting from anoxia of the central nervous system, are deceiving. Signs such as mild cyanosis and slight liver enlargement are likely to go unnoticed in infants.

To our minds, an important reason for misinterpreting rapid heart action in the young is the infrequency with which electrocardiographic studies in this age group are ordered. The average pediatrician is not sufficiently electrocardiographic-conscious. Although the differential diagnosis of paroxysmal tachycardia can be suspected clinically, it can be established with certainty only from the electrocardiogram. It is well to remember that a shifting auricular flutter can give a deceptive ventricular rate. Because of technical difficulties encountered in recording electrocardiograms in the very young, the tracings obtained are not always satisfactory, thus discouraging clinicians who will then be satisfied with only an occasional electrocardiogram. With care and patience, however, excellent electrocardiograms can be obtained in any age group. It should be emphasized that if electrocardiographic studies are limited to the paroxysms of tachycardia, without further investigation when the heart rate is slower, the diagnosis of the Wolff-Parkinson-White syndrome will be ignored. The high incidence of the Wolff-Parkinson-White syndrome reported in the older age groups is undoubtedly due to the more frequent use of electrocardiograms in these age groups.

It is interesting to note that when an infant develops paroxysmal tachycardia the ventricular rate is likely to be dangerously extreme. Edeiken[12] in a review of the literature of extreme tachycardia, those over 300 per minute, collected seventeen cases, and of these twelve occurred in infancy. The fastest human ventricular rate on record, a rate of 365 per minute, was reported in an infant.[2] There has been no satisfactory explanation for this tendency to extreme tachycardia in infancy, but it is possibly related to the size of the muscle fiber and glycogen content of the A-V node. According to Lewis,[13] the length of systole, duration of the refractory period, and the rhythmicity of

the various center of the heart are inversely related to the size of the muscle fiber and glycogen content.

The therapeutic approach to the Wolff-Parkinson-White syndrome deserves some comment. Once a diagnosis of paroxysmal tachycardia is established, effective measures to restore normal rhythm should be instituted. Procrastination may lead to circulatory failure or sudden death. If the tachycardia is of the supraventricular type, vagal stimulating drugs are indicated. Pressure on the carotid sinus or eyeballs is of no value in this age group. According to Hubbard,[1] the most effective drug in paroxysmal tachycardia in infants is digitalis. In our patient, however, digitalis in the doses used was ineffective in restoring a normal rhythm at a critical time, and reliance had to be placed on a drug with a faster and stronger vagal action, namely, Mecholyl. The intravenous use of acetylcholine-like drugs is considered dangerous. In our patient it was lifesaving, and a similar experience in two other infants has been reported recently by Gibson.[14, 15] The tachycardia in the Wolff-Parkinson-White syndrome, in rare instances, may be of the ventricular type,[16, 17] in which case quinidine is the drug of choice. Digitalis is generally considered contraindicated in ventricular tachycardia,[18] and without the aid of electrocardiograms, it is practically impossible to identify this type of tachycardia. On clinical grounds, therefore, when confronted with a tachycardia, the exact nature of which has not been established, quinidine in preference to digitalis should be used since quinidine is also effective in the supraventricular type of tachycardia.[19] Unfortunately, quinidine sulfate was not tried on our patient. From a prophylactic standpoint, quinidine in preference to digitalis is also the drug of choice. It has been demonstrated that quinidine, if used in sufficient strength, will reverse the abnormal electrocardiographic pattern in this syndrome to normal.[20-24] It has been postulated that quinidine sulfate has a greater affinity for the anomalous pathway in the Wolff-Parkinson-White pattern, depresses it, and thus allows transmission of the sinus impulse through the normal pathway. Digitalis, on the other hand, by depressing the A-V node tends to divert the impulse through the aberrant pathway, thus exaggerating the abnormality. In repeated experiments in a patient with the Wolff-Parkinson-White syndrome, Fox, Travell, and Molofsky[21] were able to produce uniform widening of the abnormal QRS complex by means of digitalis. In our patient, digitalis, in the doses used, was ineffective in restoring a normal electrocardiographic pattern (Fig. 2), and failed to prevent further paroxysms of tachycardia.

SUMMARY

1. A fatal paroxysmal tachycardia in a newborn infant with the Wolff-Parkinson-White syndrome is reported.

2. Most instances of the Wolff-Parkinson-White syndrome have been reported in the early decades of life. To our knowledge this is the youngest patient reported with this syndrome. This high incidence in the young suggests that the cause of the abnormal electrocardioghaphic pattern may be a congenital defect of the conducting mechanism.

3. Digitalis was ineffective in preventing the paroxysms of tachycardia in our patient. The drug of choice is probably quinidine sulfate.

4. Paroxysmal tachycardia is not rare in infants. In the differential diagnosis of a rapid heart action in the very young, the Wolff-Parkinson-White syndrome should be considered. The more frequent use of electrocardiograms in infants, both during and after paroxysms of tachycardia, is recommended.

The authors wish to thank Sister Maria Dolorosa, Sister Maria Brendan, and Dr. Stephen Voong of St. Vincent's Hospital, Staten Island, N. Y., for their generous cooperation.

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A CASE REPORT OF THE USE OF COMBINED DOCA AND ASCORBIC ACID IN A 12-YEAR-OLD CHILD WITH RHEUMATOID ARTHRITIS

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AN OPPORTUNITY to appraise the new treatment for rheumatoid arthritis suggested by Lewin and Wassén[1] presented itself with the admission of a 12½-year-old female to the Pediatric Service of the University Hospital. After a comprehensive survey of the pediatric literature we have been unable to find any reference to the use of desoxycorticosterone acetate and vitamin C in the treatment of rheumatic arthritis in children to date.

Widespread interest has been stimulated in the therapy of rheumatic arthritis by the publications of Hench and collaborators[2] in the successful use of ACTH and cortisone. Since ACTH and cortisone are difficult to obtain, expensive, and often attended with toxicity, we felt that this case afforded us the opportunity to evaluate the desoxycorticosterone acetate and vitamin C method of therapy.

CASE HISTORY

The patient is a 12½-year-old white female who was admitted to the Babies' Ward of the University Hospital, New York University-Bellevue Medical Center on Jan. 30, 1950, with the chief complaint of pain in the neck and hands for three months' duration and swelling of the ankles intermittently for a period of three years.

Her past history revealed that she had had the usual childhood diseases. At the age of 9 years a questionable diagnosis of rheumatic fever was made, for which the child spent three months in bed.

The present illness had its onset three months prior to admission to the hospital when she developed pains in her wrists and fingers. Later these symptoms spread to involve her neck. She was hospitalized at another institution where a diagnosis of arthritis was made. So far as we know no form of treatment was instituted, and for the past two months the signs and symptoms referable to the parts mentioned have progressed.

Physical examination revealed a poorly nourished, depressed, and unhappy white female who was very cooperative and friendly. Weight was 67½ pounds, pulse 98, respirations 20, and temperature 98.6° F.

Except for the following positive points, the remainder of the physical examination was essentially negative.

Neck: The neck is held in a slightly flexed, strained position. Flexion can be accomplished with ease. Extension is limited to about 30 degrees; rotation to the right limited to about 30 degrees and to the left 50 degrees.

Hands: There are swellings of both the proximal and distal interphalangeal joints that are nontender to palpation. Definite crepitation is present on passive movement of the affected joints.

From Feb. 8 through March 10, 1950, she received twenty-nine physiotherapy treatments consisting of tank treatments with motion of the involved joints. Although slightly improved subjectively during this period there was

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no real objective improvement according to the physiotherapist. Because of the unappreciable results thus obtained it was decided to institute therapy suggested by Lewin and Wassén.[1] Physiotherapy was discontinued. The various procedures listed in Table I were done prior to therapy.

TABLE I

CBC	WEIGHT (POUNDS)	BLOOD PRESSURE	SODIUM	POTASSIUM	URINARY SUGAR	SEDIMENTATION RATE	BLOOD CHEMISTRY
Before Treatment							
R.B.C. 4.5 mil.	68	3/8/50	3/8/50	3/8/50	Neg.	Average	Uric acid 1.8 mg.
Hb. 12.5 Gm.		118/78	121.3	4.2		8	%
W.B.C. 5,900			meq.	meq.		mm./hr.	Inorganic phosphorus 3.2 mg.
P 75							%
L 22							Total calcium 11.2 mg. %
M 3							Alkaline phosphatase 4.9 Bodansky units
During Treatment With Doca and Ascorbic Acid							
W.B.C. 4,850	68	3/10/50				3/7/50	
P 53		100/80				8	
L 33	69½	3/11/50				mm./hr.	
M 14		128/98					
	67½	3/15/50	3/15/50		Neg.		
		108-118	129 meq.	5.7 meq.	3/16/50		
		70 70			Neg.		

The method of treatment was as follows:

An intramuscular injection of 2.5 mg. of desoxycorticosterone acetate (Percorten)* was given and then followed in five minutes by an intravenous injection of 500 mg. of ascorbic acid in 1 c.c. of saline. In addition, the child was offered a low sodium diet to avoid any possible effect of Doca on salt and water retention.

RESULTS

Within ten minutes after the intravenous injection of ascorbic acid marked beneficial effects were noted. The child appeared more animated and volunteered the information that her joints felt less stiff and that she could move them more freely. Measurements† of the affected joints made ten minutes and four hours after the treatment were compared with measurements made directly before treatment (Table II). All of these measurements were performed by one of us (F. R. K.). Treatment was repeated twenty-four and ninety-six hours after the initial injection. The results are also recorded in Table II. It can be seen that there was definite increase of range of motion—compare italic figures in Table II.

The sedimentation rate showed no change, no electrolyte disturbance, no urinary sugar. There was no evidence of edema or gain in weight. In short, none of the toxic effects observed with ACTH and cortisone were noted.

Since we were unable to continue treatments in the hospital because the patient lived at a great distance from the hospital and because of her anxiety to get home, the child was sent home on Pregnenolone,‡[3] 100 mg. three times daily.

*One-half of the adult dose recommended by Lewin and Wassén was decided upon because the optimum dose in children had not been established.

†Measurements were made by means of an arthrometer (Whittier).

‡Wyeth Incorporated, Philadelphia, Pa.

TABLE II. RESULTS OBTAINED WITH DOCA AND ASCORBIC ACID

		3/9/50 BEFORE	AFTER 10 MIN.	AFTER 4 HR., 15 MIN.	3/10/50	3/13/50	3/14/50 BEFORE	3/14/50 AFTER
RIGHT								
Wrist		*58*	65	66	65	59	60	*69*
Thumb	Proximal	*57*	54	54	56	60	52	*60*
	Distal	*23*	29	36	27	24	23	*30*
Index	Proximal	*66*	73	72	81	67	75	*76*
	Distal	*25*	34	36	29	27	25	*28*
Middle	Proximal	*55*	65	68	66	65	72	*66*
	Distal	*40*	52	52	51	44	40	*52*
Ring	Proximal	*68*	78	82	85	76	85	*84*
	Distal	*34*	43	48	47	40	45	*43*
Little	Proximal	*70*	87	77	84	83	77	*80*
	Distal	*36*	42	45	43	30	39	*45*
LEFT								
Wrist		*63*	72	72	72	73	66	*78*
Thumb	Proximal	*51*	51	53	55	53	55	*54*
	Distal	*32*	47	43	56	53	44	*46*
Index	Proximal	*51*	68	63	69	69	70	*75*
	Distal	*34*	30	34	35	32	28	*29*
Middle	Proximal	*62*	72	73	70	77	72	*78*
	Distal	*52*	48	54	48	45	49	*49*
Ring	Proximal	*81*	83	83	87	85	83	*90*
	Distal	*45*	46	41	44	39	41	*45*
Little	Proximal	*66*	66	63	78	63	65	*73*
	Distal	*49*	52	55	50	54	58	*62*

Note: Measurements are in angle of flexion.

SUMMARY

A child with rheumatic arthritis was treated with Doca and ascorbic acid. It might be well to mention that this treatment in adults has been the subject of controversy,[4, 5, 6] Objective measurements which were recorded indicate that there was improvement in this case, which was maintained with only slight regression. We are aware of the fact that definite conclusions cannot be drawn on the results obtained with this type of treatment in one case but our results are encouraging.

It is hoped that this case report will stimulate further interest in investigation of this type of therapy in order that it may be more fully evaluated. Speculation arises as to whether the effects were due to the combined Doca and ascorbic acid, or to the ascorbic acid therapy alone.[7]

We wish to thank Dr. Charles Varga and Miss Sonja Kramarsky for their asistance in the preparation of this paper.

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ADDISON'S DISEASE IN A NEGRO CHILD

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ADDISON'S disease in infancy and childhood is a relatively unusual condition. In a critical review published in 1946, Jaudon[1] found in the literature sixty-two cases of Addison's disease in children under the age of 15 years which he classified as proved, 23 which he classified as probable, and 15 as doubtful. He found no cases reported in Negro children and only six of the proved cases were in children under the age of 6 years. We therefore present this case of a 2½-year-old Negro girl whose clinical course and autopsy findings were typical of an acute crisis of Addison's disease.

A survey of the literature since Jaudon's review[1] reveals an increasing reporting of cases of adrenal cortical insufficiency in the newborn infant. Many of these cases have occurred in connection with the adrenogenital syndrome. Zuelzer and Blum[2] collected seventeen such cases from the literature, three of which had been included as proved cases and four as probable cases in Jaudon's review.[1] Zuelzer and Blum[2] added four cases of their own. In addition to the twenty-one cases thus reviewed and reported, there are recent reports of the same condition by DeJong and Schaberg[3] (two cases), Chenoweth[4] (one case) and the New York Hospital group[5] (one case). Other cases of adrenal insufficiency occurring in the newborn infant but not apparently associated with the adrenogenital syndrome have been reported by Larguia, Vazquez, and Vidal[6] (one case), Jaudon[7] (five cases), Sikl[8] (one case), Roberts[9] (three cases), Moore and Cermak[10] (one case) and Provenzano[11] (one case). Of ten cases reported by Allibone, Baar, and Cant,[12] some were probably associated with the adrenogenital syndrome and some were not. In contrast to the frequency of these reports of adrenocortical insufficiency in the newborn infant, we are able to find only three cases reported in older children since 1946.[13-15] None of the above cases are recorded as having occurred in Negro children or infants.

CASE REPORT

M. L. D., a 2½-year-old Negro female infant, was admitted to Dooley Hospital Nov. 8, 1948, with a chief complaint of convulsions. She was said to have been well until 4 A.M. the day of admission, when she awoke complaining of stomach-ache. About 5 A.M. she went into a generalized convulsion. When seen by her local physician an hour later she was still twitching and was given a sedative hypodermically. She vomited once, then went to sleep. Twice during the day she awoke twitching and received further sedation. On the second occasion she was referred to the hospital.

Past history revealed a normal spontaneous birth on May 3, 1946. Records obtained from this hospital state that her birth weight had been 2,700 Grams and she had gained on evaporated milk formulas to 2,980 Grams by the time of discharge May 12. "She was admitted again on June 1, 1946, with a history of refusing formula and weight loss. The infant was in extremis, being dehydrated and acidotic on admission. Weight was 2,500 Grams; temperature, 106° F.; W.B.C., 29,000; R.B.C., 5.85 million; hemoglobin, 18.0 Gm. The infant was

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given clyses, sulfaguanidine, penicillin, and formula of Biolac. She improved gradually. On June 6, 1946, she developed cellulitis of the arm and pus from this, on culture, revealed a gram-negative bacillus. She was discharged June 29, 1946. The child was seen in August, 1946, for her three months' examination. She had gained well and was apparently in good health."

The child had been well since that time. The family history was essentially negative except that the father had had "fits" in childhood.

Physical examination revealed a well-developed and well-nourished 2½-year-old Negro female infant who appeared acutely ill, moderately dehydrated, comatose, and who was having a left-sided clonic convulsion which soon became generalized. The temperature was 104° F., pulse 140, and respirations 32. No abnormal pigmentation was noted on the skin. The pupils were dilated and reacted poorly to light. The right tympanic membrane showed moderate diffuse reddening and dullness. The light reflex was broken and the landmarks obscured, but no definite bulging was noted. The left tympanic membrane showed slight injection of the malleal vessels. The pharynx and anterior tonsillar pillars were moderately injected. The neck was flaccid. The chest was clear and resonant except for transmitted rhonchi. The heart was normal, the abdomen slightly distended. Extremities were normal. Tendon reflexes were obscured by generalized convulsion. No pathological reflexes were noted.

Fig. 1.—Detail of x-ray of chest and abdomen (slightly retouched) showing granular calcifications in both adrenal glands.

Laboratory data on admission were: hemoglobin, 13 Gm.; W.B.C., 26,100 with 75 per cent polymorphonuclears, 20 per cent lymphocytes, 4 per cent monocytes, 1 per cent basophiles. Serum bicarbonate was 14 meq. per liter, serum chloride, 104 meq. per liter. Spinal fluid was clear under no increased pressure; there were no cells, there were 15 mg. protein, 56 mg. sugar, 126.5 meq. per liter chlorides. Urine showed 3 acetone and 3 to 4 white blood cells per high power field. Blood culture was negative.

She was placed on penicillin therapy and by the following morning her temperature had dropped to 100° F. However, she was more deeply comatose and had lapsed into a shocklike state, with the peripheral pulse unobtainable. Fluids were begun by vein, then by hypoclysis, and 700 c.c., including 500 c.c.

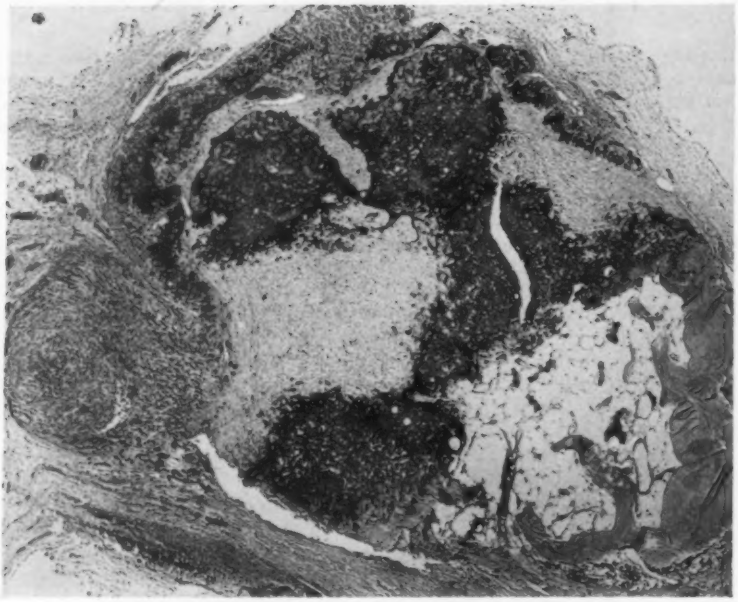

Fig. 2.—Section through the left adrenal gland. There is a small island of cortical tissue at the left of the photograph, areas of fibrosis and irregular calcification in the center, and heteroplastic bone with marrow formation at the lower right.

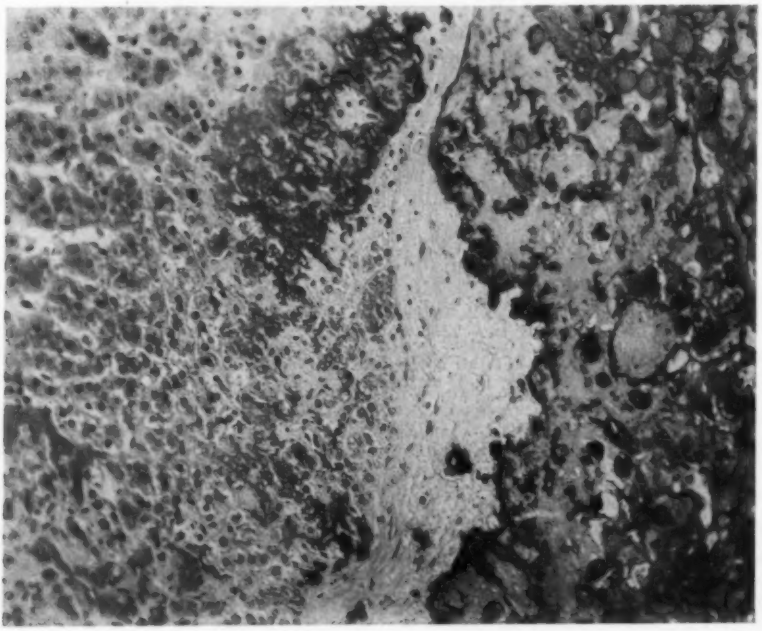

Fig. 3.—Detail from left adrenal gland. Normal cortical structure is seen at the left, fibrosis and calcification on the right.

of M/6 sodium acetate, were given the morning of Nov. 9, 1948. Sometime during that morning (the exact time in relation to the fluid therapy is not recorded) laboratory studies showed a blood nonprotein nitrogen of 99 mg., sugar 70 mg., serum bicarbonate 18 meq. per liter, sodium 141 meq. per liter, chlorides "insufficient serum to determine."

The patient continued in shock and by 4:30 P.M. November 9, the heart sounds were very weak at a rate of 200, and respirations were shallow at a rate of 81. The extremities were cool and the patient failed to respond to stimuli. At this time bilateral basal râles were heard, and an x-ray of the chest was taken (Fig. 1). The report, which was not received until after the patient died a few hours later, was as follows: "The heart was small and ptotic in type with no widening of mediastinum. There was very slight prominence of the bronchovascular markings, particularly in the left lower lung. The stomach was distended with gas and the entire large intestine was filled with gas. There were irregular granular calcifications on both the right and left side of the tenth and eleventh dorsal vertebrae. On the right these deposits covered an area 1.8 cm. in height and 1 cm. in width and on the left an area 2 by 1.2 cm. They were in the region of the adrenals. The kidneys and adrenals were not sharply outlined." At 7 P.M. a continuous intravenous drip of lactate-Ringers and 5 per cent dextrose was begun. The patient received about 650 c.c. of this, but continued her downhill course and died at 12:45 A.M. Nov. 10, 1948, thirty hours after admission.

At autopsy the major pathologic findings were related to the adrenal glands (Figs. 2 and 3), which were described as follows: "Gross weight: left 1.5 grams; right, 1.5 grams. Both adrenal glands are small, fairly firm, and cut with a gritty sensation. The external surfaces are irregular, the right being yellowish and the left reddish-gray. Microscopic: Much of the adrenal tissue is replaced by fibrous tissue, numerous areas of calcification, and a few areas of bony spicules in which are found a fatty marrow structure with a few myeloid cells. This change causes almost complete loss of medulla and a large portion of the cortex. Many hemosiderin deposits are present. The remaining cortical cells are moderately depleted of lipoid materal. The vessels are moderately congested. The capsule has an increased amount of fibrous tissue and several focal hemorrhages are seen."

Other autopsy findings were small areas of focal bronchopneumonia and moderate diffuse fatty metamorphosis of the liver. The brain and spinal cord were normal except for moderate congestion of the vessels.

DISCUSSION

This patient apparently had had partial destruction of the adrenal glands by septicemia and hemorrhage at the age of one month. She had apparently done well, however, until an acute Addisonian crisis was precipitated by acute otitis media and bronchopneumonia. The true nature of her condition was not appreciated and she did not receive adrenal cortical therapy.

SUMMARY

A case history is presented of a 2½-year-old Negro female infant who died in what appeared to be an acute Addisonian crisis precipitated by otitis media and bronchopneumonia. At autopsy most of the adrenal gland tissue had been replaced bilaterally by fibrosis, calcification, and heteroplastic bone formation. This destruction of the gland is believed to have resulted from a septicemia at the age of one month.

To our knowledge this is the first case of Addison's disease ever reported in a Negro child.

We wish to express our appreciation to Dr. John E. Rayl, of the Department of Pathology, who performed the autopsy.

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Clinical Conference

CONFERENCE AT THE CHILD GUIDANCE CLINIC, BROOKE GENERAL HOSPITAL, FORT SAM HOUSTON, TEXAS, NOV. 2, 1949

LIEUTENANT COLONEL LEO J. GEPPERT, PEDIATRICIAN-IN-CHIEF

INTRODUCTION

COLONEL RAWLEY E. CHAMBERS (Chief, Neuropsychiatric Service).—The Child Guidance Clinic at Brooke General Hospital was established and open to receive patients in August, 1948, after more than a year of planning and consideration. Shortly before this time the military personnel situation had stabilized, officers with training in mental hygiene work became available, and suitable physical facilities were provided by the hospital commander. It was not by accident that these facilities were located in close proximity to the Pediatric Clinic. The need for mental hygiene activities to serve the many minor dependents of military personnel in the vicinity of San Antonio is obvious. There is no similar service in the civilian community. An important need for well-rounded training of neuropsychiatric and pediatric residents exists. The opportunity for participating in the welfare activities of this civilian community is great. In the history of military medicine in the United States, no such specially organized activity has previously been available within the military service.

In accordance with the neuropsychiatric team concepts the basic composition of the clinic's staff consists of a highly trained clinical psychologist, a military psychiatric social worker, and a psychiatrist. Other members are Red Cross psychiatric social workers, medical officers in training, psychiatric nurses, a clerical staff, and volunteer semiprofessional workers. A pediatric resident is present during all clinic sessions, and attends weekly case conferences. These conferences are held by the clinic staff to determine allocation of patients, to summarize all available information, to formulate treatment plans, to follow patients' progress, and to effect final disposition. Joint conferences such as this are held monthly to present a more complete picture of a few selected patients. The operation of the clinic will be explained by its operating chief.

MAJOR FREDERICK A. ZEHRER (Clinical Psychologist).—The purpose, organization function, and routine of this Child Guidance Clinic was described in the Army Medical Bulletin.[1] For the benefit of the visitors, the standard

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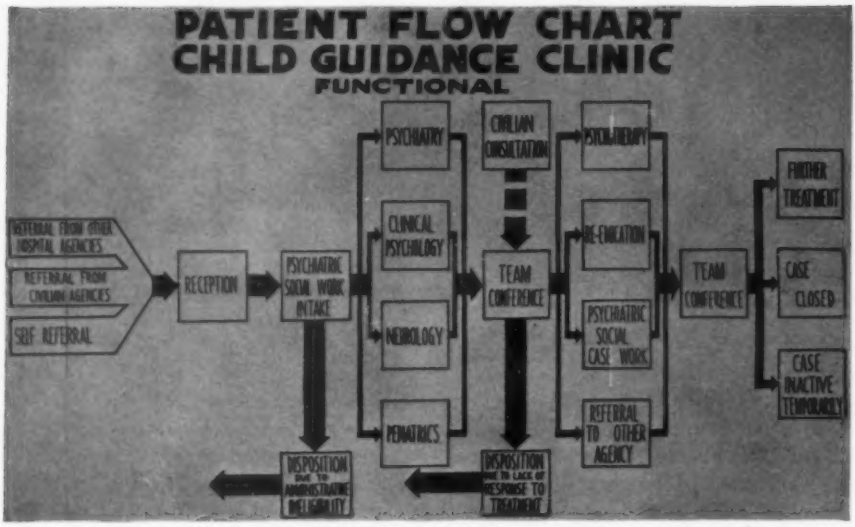

Fig. 1.

operating procedure of the Child Guidance Clinic is as follows: (Fig. 1.) About 55 per cent of our referrals come from the Pediatric Clinic. About 12 per cent come from civilian agencies, and about 27 per cent are self-referrals from families eligible for service by virtue of being dependents of active duty military personnel. At the first appointment the family is interviewed by a psychiatric social worker. Pertinent material in the case is then summarized by the social worker. To avoid duplication of effort and to discover areas which need exploitation, this material is reviewed by the professional staff before the second visit. In following sessions the psychiatrist sees the parents to make his own evaluation and further exploration. He also sees the child briefly and does a thorough neurological examination. On the second visit the child is also seen by the clinical psychologist so that he can begin clinical psychologic evaluation of the individual, including his special abilities, any special defects he may have, make a brief appraisal of his emotional state, and determine how well he is functioning in terms of use of his abilities. Following this visit, a team conference is held. The referring pediatrician attends this conference, where all available information is pooled. At that time a decision is made as to whether or not we can be of help in this particular situation. If this decision is in the affirmative, plans for psychotherapy, re-education of parents, or recommendations for remedial reading or speech training are inaugurated. The parents are made to feel that they are part of the total situation and that it is not the child alone who has the problem. In some instances, referral is made to another agency better equipped for a particular reason to follow through on a given case, as for example a child who needs institutionalization. Periodic staff conferences are held on each case. At these staff meetings changes in therapy, en-

vironmental manipulations, or decision to close the case are agreed upon. Some cases are allowed to become inactive to let time play a part in the therapeutic program. We have found it most useful for the pediatric resident to serve directly in a psychiatric role with the support and guidance of the clinic staff provided by repeated conferences concerning his patients. He thus learns to do simple therapy as well as preventive psychiatry. The more difficult cases are transferred to one of the psychiatrists. Personnel is sufficient for a double team so that cross referrals may be made when indicated. The inclusion of the pediatric residents provides a basis for a good working relationship between the services.

The two cases about to be presented represent a cross section of the procedures and activities of the Child Guidance Clinic.

Case 1. Ulcerative Colitis

LIEUTENANT COLONEL LEO J. GEPPERT (Chief, Pediatric Service).—This patient has been followed at this hospital for more than two years. During the first half of this period the Child Guidance Clinic was not in existence. I believe that this case demonstrates clearly the difficulty in handling the psychosomatic aspects of pediatric practice without such a clinic, even though the basic psychologic difficulty is apparent.

Chief Complaint.—This 12½-year-old white male child was first brought to the pediatric clinic on July 2, 1947, because of intermittent abdominal pain and mild diarrhea.

Family History.—His father, aged 38 years, is retired for a nonfamilial physical disability. His mother, aged 36 years, is living and well. One sister, aged 7½ years, is living and well. The maternal grandfather is known to have amebic dysentery. There is no other history of familial disease.

Past History.—The patient was a product of a full-term, normal delivery, May 5, 1937. Birth weight was 8 pounds. There was considerable vomiting during the neonatal period, but weight gain was satisfactory. Breast feeding was discontinued at age 6 weeks. Formula was given until one year of age. His general health has been excellent. He has had pertussis, measles, chicken pox, and was hospitalized for one week in January, 1941, for burns, and again in 1946 for influenza.

Present Illness.—This patient's present illness began approximately one year before admission, when he began to complain of vague, intermittent, mild "stomach ache." During this time fecal urgency was also noted. On May 24, 1947, he had a rather severe attack of abdominal pain. During the next week the patient had intermittent attacks of rather severe, cramping abdominal pain. The pain would last for several minutes and then subside. There was no associated vomiting or diarrhea.

On June 1, 1947, the patient visited his grandfather's ranch in Mexico. On June 10, 1947, he had another attack of rather severe abdominal pain which was relieved by an enema. He recovered rapidly with bed rest, but when activity was resumed, he had a third attack of abdominal pain. Following this attack,

he began, spontaneously, to have four to five greenish-yellow stools a day. Blood and mucus were noted in these stools and occasionally he passed only blood and mucus. Tenesmus was marked. Fever was not noted.

Upon his return to the United States, June 28, 1947, the stools became more formed, but he continued to have two or three bowel movements each day and blood was regularly noted in his stools. His mother did not consider his illness very severe. She brought him to the Pediatric Clinic primarily to ascertain the advisability of allowing the patient to accompany the rest of the family on a fishing trip the following day. She was also concerned about the possibilitiy of her son having contracted amebic dysentery from the grandfather.

Physical Examination.—The patient at that time was an active, exceptionally well-developed, somewhat obese, intelligent, apparently healthy white male child, 10 years of age. Height was 53 inches. Weight was 88 pounds. Routine physical examination revealed no abnormalities, but proctoscopic examination revealed minute hemorrhagic ulcers in the lower bowel. Careful and repeated examinations of stools for ova and parasites demonstrated only cysts of *Giardia lamblia.* On culture, *Salmonella oranienburg* was isolated from the stool.

Course.—Although the patient was not acutely ill, he was admitted to the Contagious Disease Ward where he received intensive therapy with streptomycin and Sulfathaladine. After two weeks, he became asymptomatic and repeated stool cultures were reported as negative. A course of Atabrine was then given with disappearance of the Giardia. He had no fever during his hospital stay. He lost 2½ pounds during his two weeks in the hospital. Cultures being negative, and the proctoscopic examination revealing no evidence of the hemorrhagic ulcers previously described, the patient was discharged in July, 1947, with a diagnosis of enterocolitis, acute, moderate, due to *S. oranienburg.*

The patient was readmitted to the hospital on Aug. 8, 1947, because his symptoms had recurred immediately after discharge from the hospital. He had lost an additional 5 pounds in the two weeks at home. He had no fever.

Physical examination was again negative, except that the patient now appeared to be chronically ill. Proctoscopic examination again showed the mucosa of the bowel to be hyperemic and hemorrhagic. A few ulcers were noted. A barium enema was reported as showing complete absence of haustral markings with a fuzzy appearance in the mucosal pattern. The picture was suggestive of ulcerative colitis. Chest x-ray was negative. Repeated examinations of the stool for ova and parasites were negative. Stool cultures were negative. Red blood count was 5.2 million, white blood count 7,800, hemoglobin 13 Gm., polymorphonuclear cells 74 per cent, lymphocytes 26 per cent, reticulocytes 0.8 per cent, platelets 230,000. Urinalysis was negative. Cephalin flocculation and thymol turbiditiy tests were negative. Prothrombin time was normal. Total protein was 8.2, albumin 4.8, and globulin 3.4.

The patient was treated with oral streptomycin and Sulfathaladine. In a few days stools again became normal in consistency and number. Blood and pus could no longer be detected in his stools.

He was again discharged Sept. 2, 1947. Because of recurrence of symptoms in the home environment, psychiatric consultation was arranged.

DR. ALFRED HILL (Civilian Consultant in Neuropsychiatry).—My contact with this case consisted of one visit with the boy in September, 1947, in the midst of the development of the severe phase of his illness, one visit with the father during that same month, and fifteen visits with the mother in January, February, and March, 1948. Acute psychosomatic illness in a child is practically never produced by a circumscribed series of events in the life of that child alone; almost invariably, severe psychosomatic illness in a child is produced by illness of more than one generation. I think you will see in this case that we have a three generation problem. The background which this patient derived on the father's side is as follows: The paternal grandparents belonged to one of the leading families in a small town in a southern state. It was essentially a matriarchy, with the grandmother dominating the father and in turn the children. The marriages of his uncles and aunts had been broken up, presumably by the interference of the grandmother. One of his aunts was an alcoholic. The father of the patient was dominated by his mother. We will see to what extent as we go along. The background on both sides of the family has been consistently of a better-than-average cultural, economic, and educational level for three generations. The mother's background is as follows: At the present time the maternal grandfather is about 70 years of age and the maternal grandmother about twenty years younger. The grandfather is a rancher in Mexico. The grandmother lived in the Rio Grande Valley. The family was therefore seldom together. The patient's mother was reared principally by a housekeeper and by a "motherly soul" who lived next door. The maternal grandmother was employed in a local concern. The mother's comment about her background in her own words was, "We children grew up like ragweeds." One of the earliest things she remembers about her life was the fact that her abdomen would swell and she was unable to eat on Sundays when her mother was at home. This was approximately twenty-eight years before the appearance of our patient on the scene. She describes her mother as being an excellent traveling companion but very impractical. She was "on the go" all the time and was unconcerned about the elements of daily life such as preparing meals on time. The patient's mother went to two different colleges, each for a year. In 1933, with this background, and without any particular previous male companionship, she married her husband and the father of the patient.

The boy was born three years after the marriage. Toilet training was begun at the age of 2 months. Suppositories were frequently used. Following the period of infancy various medications and enemas were given for the relief of constipation. The mother was quite disturbed because the father would not accept responsibility for toilet or other training of his son. Five years after the birth of the patient a sister arrived. Following this delivery, the mother had a period of panic, evidently an acute neurotic anxiety state, for four or five months. The father was absent during this period and the mother was cared for by her mother-in-law. Following the birth of the daughter, as we go along

in the history, we find that the mother identified herself with her daughter to the exclusion of her son. The daughter had the same likes and dislikes; she liked to dress up, and was commented upon as being cute, lovable, etc. The patient by this time had become intensely jealous. He developed chronic thumb-sucking, temper tantrums, crying spells, and negativistic reactions. He would scream with tension when favor was shown his sister. He began to try to dress as his sister did. He stole his mother's perfume and wore her slippers; wore her clothing, and tried to identify himself with the sister in every respect. He also began to have difficulty in school. He frequently changed schools, since the family moved six times in ten years. He developed habits which disturbed his mother. On one occasion he was accused of having stolen a few pieces of change, which considerably upset the family.

The only time I saw this boy he was medically too ill for much psychotherapy to be attempted. I, therefore, tried to work with the parents. The father was working at an assignment which required twelve hours a day, seven days a week, so he had no time with the family. He recognized that this was not desirable for the family and tried for two or three weeks to spend time with the boy, but soon gave up the effort. In October, 1947, it became necessary to remove the boy from military school because of fecal incontinence. He was having nine to ten watery stools a day. The stools contained blood and pus. Abdominal pain was noted prior to and during bowel movements. By December, 1947, the patient lost 28 pounds and appeared chronically ill. At this time the mother came voluntarily for help for herself, and presented as her first symptom the fact that she was having indigestion. She was only slightly disturbed about the condition of her son, but was very concerned about her own symptoms and anxiety.

After three or four hours she showed her first real emotion. This was when she was telling me about the rejection she had received as a child at the hands of her mother. At this time, the paternal grandmother, who was recovering from a stroke, was brought into the home. The home at this time consisted of a five-room apartment occupied by the father (the father being away twelve hours a day, seven days a week), the mother, the patient, the 5-year-old sister, and a partly paralyzed but still domineering and demanding grandmother. The mother of the patient was so antagonistic toward the mother-in-law, who was still trying to interfere with all the family affairs, that she tried to force her husband to move his mother out. There was so much conflict in the home and the patient's mother was so resentful of her mother-in-law that she did not eat with the family. She also decided that if her husband would not move his mother out of the crowded apartment she would not sleep with him. For the next two months the father shared a bed with the patient. To further complicate the situation, the alcoholic sister of her husband called frequently at night disturbing the family rest. At this point, the father, who was very disturbed at his wife's indifference to him, left the family entirely.

At this time the pediatrician will bring us up to date on the patient's physical condition.

COL. GEPPERT.—By March, 1948, the patient's condition had become very poor, therefore hospitalization was again recommended. In addition to weight loss of over 30 pounds, pallor and weakness had become very marked. Proctoscopic examination showed the mucosa of the rectum to be cobblestone in type, markedly granular, and very friable, with free bleeding merely from passage of the proctoscope. Microscopic examination of the exudate showed 4-plus white blood cells, 2-plus epithelial cells, and one-plus mucus. Repeated examinations of stools for amebae and parasites were negative, as were cultures. Small bowel studies showed only increased motility, but barium enemas revealed a complete lack of haustration throughout the colon. X-ray findings were interpreted as typical of ulcerative colitis. X-rays of sinuses showed maxillary sinusitis. Agglutinations for typhoid, paratyphoid, tularemia, brucella, and Proteus X_{19} were normal. Urinalysis was negative. Sedimentation rate was 32 mm. corrected. Red blood count was 4.5 million, hemoglobin 90 per cent, hematocrit 45 packed cell volume, white blood count 9,350, polymorphonuclear cells 61 per cent. No eosinophiles were seen on nasal smear, and no evidence of allergic factors could be elicited.

The patient's course and response to therapy had been so poor up to this time that serious consideration was given to the advisability of performing an ileostomy. However, with intensive supportive therapy, including multiple transfusions, the patient improved fairly rapidly after hospitalization. By March 27, 1948, it was felt safe to discharge the patient from the hospital.

DR. HILL.—The mother, although previously indifferent, became frantic when the patient was almost moribund, early in the month of March. She said, "When my boy is well, I nag at him all the time because he irritates me so. When he is sick, I am oversolicitous because I feel bad about the way I have been treating him. You know, I feel as if the children were an octopus on my back. I have been spoiling my daughter; I've been doing all the things for her that I wished my mother had done for me, but too much so."

The mother, having continued psychotherapy to the extent of ten or twelve visits, began to reach considerable insight. With the cooperation of both parents, a regime was inaugurated consisting chiefly of the boy spending the majority of his time with his father. Instead of returning to school he went to live with the family on a ranch in Mexico. His father took him on frequent hunting, fishing, and airplane trips. His mother did her best to stop nagging the patient. Improvement then was progressive, the patient began gaining weight, became more active, and his appearance of chronic illness became less evident.

Summary.—In summary, then, we have in the background two immature parents each tied up with feelings of rejection by their parents in turn; each hating the effect of a mother; each working out their hostility toward their parents against each other and then in turn, when that wasn't adequate, against the children. Our patient's growth and development proceeded in this environment with the results as outlined. His course was progressively downhill until the family, and especially the mother, gained sufficient insight to provide a happier emotional background for the patient. At that point, improvement began, and has been progressive.

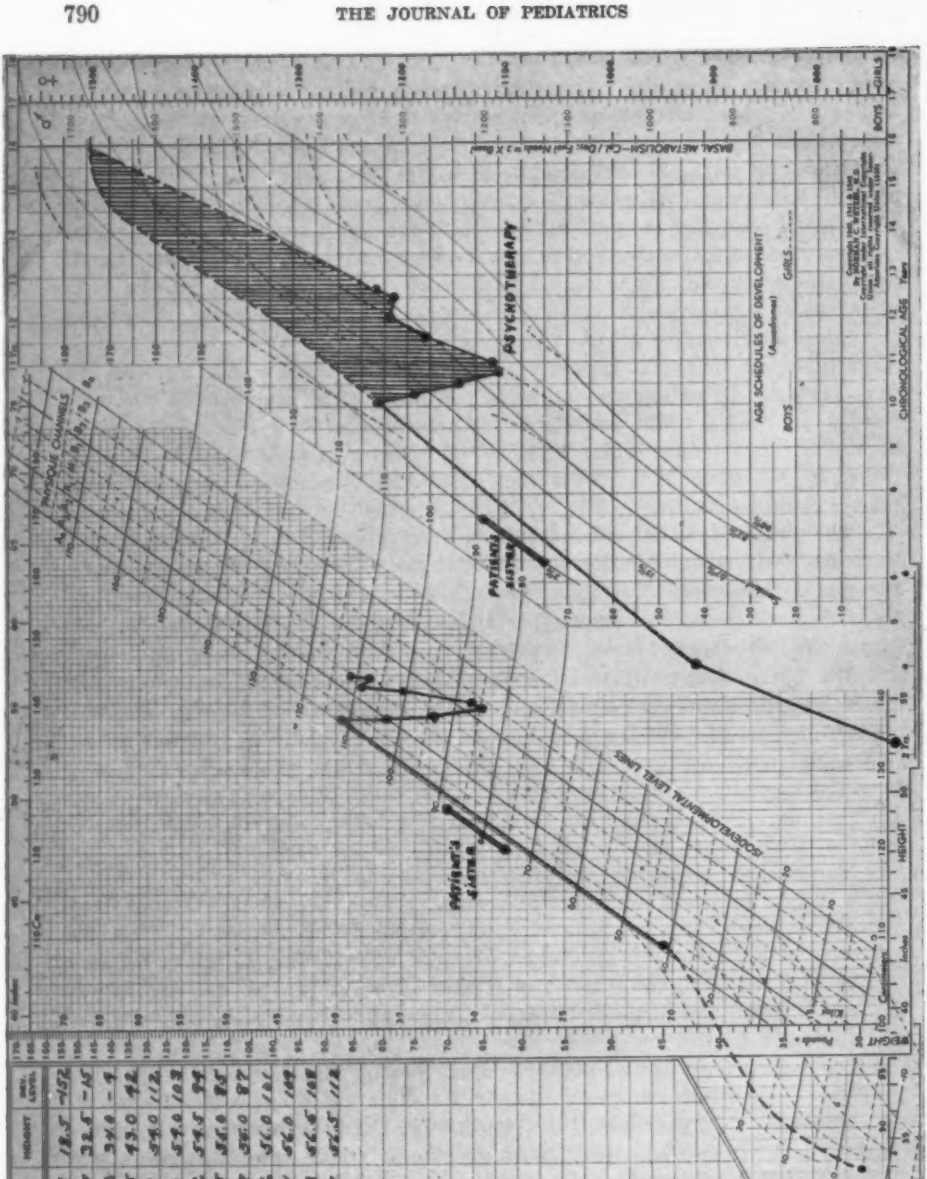
PSYCHOTHERAPY
PATIENT'S SISTER
PATIENT'S BROTHER
ISODEVELOPMENTAL LEVEL LINES
BASAL METABOLISM—Cal./Diff. Fluid Meals = 2 X Basal
AGS SCHEDULES OF DEVELOPMENT
(Academic)
BOYS
GIRLS
CHRONOLOGICAL AGE
HEIGHT
WEIGHT
DATE
AGE
WT.
HEIGHT
DEV. LEVEL
MAY 32 Blank 21.1 18.5 -152
MAR 33 21 m. 27 32.5 -45
NOV 35 34 m. 36 39.0 -9
JUNE 37 4 yr. 45 43.0 42
JUNE 38 5 yr. 53 44.0 112
DEC 39 10 y. 80 57.0 103
MAY 42 10.6 72 54.5 84
JAN 44 10.8 65 55.0 85
JUNE 45 11.1 67 56.0 82
NOV 46 11.5 76 56.0 101
DEC 47 12.0 84 56.0 109
DEC 48 12.8 93 56.5 108
DEC 49 13.4 92 56.5 118

Fig. 2.

COL. GEPPERT.—During the past year the patient has gained 20 pounds. His course as plotted on the Wetzel Grid demonstrates clearly several features of this case. (Fig. 2.) (1) It should be noted that even at the low ebb of his course, the patient's weight and physique were equal to the 67 percentile level of his contemporaries. (2) When previous data is plotted, the degree of his growth failure becomes evident. Since infancy the patient had been in Channel A_3 and his speed of development parallel to the 2 percentile auxodrome. (His sister follows a similar pattern.) (3) Channel shift from A_4 to B_2 for this patient indicates marked loss of physique. (4) During the course of his illness, even with improvement, the patient has accumulated a caloric debt of several hundred thousand. He has regained physique to the extent of reaching Channel A_4, and if previous data were not available, his growth and development might easily be considered normal. However, with plotting of previous data and the projection of his speed of development, it is evident that unless further improvement occurs, he may not overcome his growth failure before epiphyseal closure occurs.

MAJOR ZEHRER.—*Report of* PSYCHOLOGIC EXAMINATION.

The boy was 12 years, 4 months old. He was in the sixth grade at Keystone Guidance School.

Observations.—This 12-year-old boy, of good appearance, enthusiastically entered into the examination situation. He was quite self-confident in manner. His speech was very good; diction and enunciation were of high quality. His rate of response was rapid. His nails were closely bitten. He is right-handed. He stated that he likes school and gets on well with boys there. He said he formerly had difficulty with arithmetic, but now makes good progress. Affect was very good. Effort and cooperation were excellent.

Examination Data.—The revised Stanford-Binet intelligence scale, form L was used. The boy's chronological age was 12-4; his mental age was 13-8; his I. Q. was 111 (minimal). Basal year was XI and range was through year A.A. with no success at year S.A.I. Vocabulary level is at year 14 with excellent quality of definition. Comprehension, association of ideas, practical judgment, and verbal concept formation ability all at above normal levels, of good quality. However, there is evidence of inefficiency of attention of type indicative of interference of affective factors (anxiety). The I. Q. is considered to be a minimal rating due to scatter. He is above average intelligence.

Other Examinations: Rorschach, Thematic apperception test (partial), and Minnesota multiphasic personality inventory were done.

Diagnostic Impression.—This boy possesses above average intelligence. (Binet I.Q. 111.) The I.Q. is considered a *minimal* rating for prognostic purposes. His inductive reasoning and conceptual thinking is very good. Generally, he thinks in broad terms with good use of imaginative abilities. He has strong achievement drives with some overstriving. Emotionally he is fairly well developed for his age, but there are strong residuals of narcissism present. He is basically constricted and somewhat compulsive; however, this is a rather

Fig. 2.

typical pattern for early adolescents. He has rather intense anxieties and feelings of insecurity. He tends to repress his drives and apparently indulges in more than the usual amount of autistic-type thinking. This boy has difficulty in sublimating his strong drives. He has hostility feelings primarily directed toward both parents; there is much ambivalence and, no doubt, excessive guilt in his dynamics. He is hypersensitive. The over-all impression is that of a sensitive, insecure youth who is capable of empathy and will be responsive to supportive-interpretive type therapy. The area of parent-child relationships (through concurrent therapy with parents) requires consideration.

MAJOR BERNARD I. COPPLE (Chief Resident, Pediatric Service, Therapist).—This patient returned from Mexico in September, 1949. He was first seen in the Child Guidance Clinic on Sept. 16, 1949, and has spent one hour each week up to the present time with me. Our therapy to date has been only that of establishing satisfactory rapport, avoiding any approach which might cause uncertainty, frustration, or feelings of guilt. At each session the patient is encouraged to discuss freely his current interests as to playmates, roommates, entertainment, school, athletics, and so forth. The therapist has taken pains to note any mention made by the patient of members of his family. Hostility is often exhibited toward his 7½-year-old sister and toward his mother. Except to indicate that his father favors him over his sister, he seems extremely passive toward his paternal parent. One sustained interest noted each week has been that pertaining to wealth; money and Cadillacs and homes being his main interests. He shows more than average admiration and jealousy in the discussions involving these subjects. When relating his experiences at the boarding school, he shows acceptance of, and favors, the boys whom he describes as sissies. His description of sissies shows that he thinks of them as boys who act like girls. His reason for thinking that this is a desirable behavior pattern for his friends is that sissies are clean and do not get into any trouble.

After four weeks in a carefully chosen boarding school, the patient reported that he was having only one stool a day compared to over a dozen a day before his return to the United States. This was accompanied by increase of 7 pounds in weight. However, on his fifth visit, he reported that while he was having only one stool during the day, he was forced to get up at night to visit the toilet several times. His appetite had been poor, and it was noted that he was very tense. He could not sit quietly in his chair as on previous visits, but rather demonstrated many tension-releasing mechanisms. He reported that he had a new roommate with whom he was having trouble. The therapist pointed out that the roommate was two years younger than the patient, considerably smaller, and that he was therefore probably jealous of the patient's strength, size and maturity.

The sixth visit revealed that the past week had reversed the situation. The patient was now winning his arguments, playing pranks on his roommate, and had the instructors on his side. Concurrently his appetite had improved, his bowel habit had returned to the normal one a day, and he was feeling fine.

The factor chiefly responsible for present remission of symptoms of ulcerative colitis in this patient is the complete environmental change produced by placing the patient in a good boarding school many miles away from his family. In addition, we are striving to instill confidence in this patient so that he can carry his own emotional shield. The prognosis remains very guarded. This patient has been subject to twelve years of complete domination by a very aggressive mother who completely rejects and disapproves of her son.

DR. CHARLES F. MCKHANN.—I have no comment to make regarding the medical treatment of this boy. I am impressed with the history. We can't quarrel with the conclusions that have been reached with regard to what sort of a child this patient is, but I have a considerable degree of skepticism as regards the relationship between the patient's personality and his illness. Did this child develop colitis as a result of his environmental condition, or did he develop colitis as a result of an organic disease? I am frankly groping for the truth as to which is the cart and which is the horse. For example, I do not believe that any child is made allergic as a result of emotional stress, although there can be no doubt that the degree of his allergic manifestation varies with environmental changes. I realize that in the present state of our knowledge concerning the physiology of the brain we have to accept a good many things with less objective evidence than we do in other fields of medicine. It is very difficult to explain all the manifestations that one has seen in patients with ulcerative colitis on an organic basis, but it is equally difficult to explain all of the manifestations on a purely psychogenic basis. We have all seen children recover dramatically from acute illnesses after some certain type of therapy and yet remain skeptical as to cause and effect. If one could see a hundred patients such as this he would be more willing to accept post hoc ergo propter hoc, reasoning. I have no conflict with the viewpoint of the psychiatrists, but I remain skeptical about what is contributory and what is fundamental in producing this child's disease and his remissions.

COLONEL GEPPERT.—We are aware of the inadequacy of our knowledge of psychosomatic medicine and psychotherapy. However, we in practice must answer parents' questions and offer solutions to their problems to the best of our ability even though our answers are based on incomplete evidence. We cannot escape the responsibility for the treatment of a patient such as this with such weapons as we have at hand. If this child recovers with supportive medical and emotional therapy we will have attained our immediate objective. Perhaps in the process our efforts may also be rewarded by the accumulation of some of the more objective factual information for which Dr. McKhann has indicated the need.

Case 2. Bronchial Asthma Treated by Psychotherapy

CAPTAIN ARNOLD B. SCHEIBEL (Psychiatrist).—This 9-year-, 9-month-old boy was first brought to the Child Guidance Clinic in September, 1948. The case was referred from the Pediatric Clinic because of severe bronchial asthma.[2]

The mother complained also of the boy's irritable, seclusive, and occasionally bizarre behavior. He spent most of his time sitting in his rocking chair listening to the radio. He spoke infrequently, used sign language a good deal, and showed much negativistic behavior to his parents. Attendance at school was erratic because of the asthmatic attacks from which he had suffered for the past eight years. At the time of coming to the clinic, the mother estimated that the patient was spending one-half to two-thirds of his time in the childrens' ward of Brooke General Hospital. His asthmatic attacks while in the hospital were neither as severe nor as frequent as when he was at home. However, vigorous medication was still necessary when he suffered his attacks. During the first year and one-half of his life the patient had eczema and urticaria, although there was no history of allergic phenomena in the family.

The patient was a wanted child and was born about twenty months after his parents' marriage. When he was 4 years old, his father left for active duty in the Air Force and did not again return until the patient was 6 years old. During this time the patient and his mother were inseparable and the return of the father into the home precipitated repeated emotional storms during one of which the patient cried to the mother, "let's lock the door and not let him return." Relationship between the boy and his father improved somewhat in the past three years, but has never been a very demonstrative one. The birth of a baby sister when the patient was 7 years old produced no obvious disturbance. The mother has always felt that the boy was sickly, abnormal, and "slow" and had taken him to an interminable series of doctors. She was incensed by his continuing passively hostile attitude and his inability to make a better showing in school. It is interesting to note that the patient's asthmatic attacks frequently came on in the evening shortly before the mother's own bedtime. When this happened, the mother seldom slept with her husband—being obliged to spend the night in her son's room.

The patient appeared to be a small, asthenic, rather elfin-looking boy, appearing somewhat younger than his stated age. He insisted on remaining with his mother while she was interviewed by the psychiatrist. He said he would not listen, but later it was noticed that the comic book which he was supposedly reading was actually being held upside down. When asked questions he answered with single words or by sign language and for the remainder of the time sat dreamily in his chair, gazing at the opposite wall of the office. His behavior continually angered his mother who alternately threatened and spurred him on.

Psychologic examinations revealed that the boy was functionally of borderline mentality with a mental age not exceeding the average 7-year-old child entering the second grade. (Stanford-Binet I. Q. 70.) The psychologist pointed out, however, that there were strong suspicions that this was not a true indication of his basic potentialities as emotional blocking might play a role in this poor performance. Part of this opinion was based on the fact that his reading ability was equal to that of the average child starting grade 4, in which the boy was placed at that time. His comprehension and recall were also adequate

and equal to that of the average child 9 or 10 years of age. He appeared to have a well-developed fantasy life and showed many symptoms of personal maladjustment.

It was decided to place both the patient and his mother on a regimen of weekly therapeutic interviews—the boy to be seen by the psychiatrist in play therapy, and the mother by the psychiatric social worker. Because of several severe bouts of asthma, actual therapy was not started until December, 1948, three months after the initial contact with the clinic was made.

When the patient entered the playroom for the first session he was indecisive and announced that the toys were of no interest to him. After some encouragement, he finally decided to play checkers. The first time the patient made a "king" it was pointed that he was a "king on the board." He said, "No, I'm not, I'm nobody." He lost all the games and stated that he did not care about losing: "It's just the sportsmanship." It was suggested that it was all right to feel badly about losing or about being unimportant, but the patient rejected this. His feelings about his smallness were again brought out in his having the therapist build large block structures, followed by the construction of much smaller buildings of his own. The differences in size were further elaborated verbally. In the second session the patient experimented with small shows of hostility, throwing crumpled paper on the floor, messing delicately with the finger paints, and then more enthusiastically as he found that rejection was not threatened. As he gained confidence he spattered paint and tore off sheets of paper with marked enthusiasm, talking volubly the while. He came to the third session with his own set of finger paint and produced a picture of a heart inside a larger heart, writing the word "love" under it. He asked for the therapist's first name and then wrote "Arne's" above the heart. This meant "Arne's love" which the therapist obviously owed to his wife. However, in his (the patient's) home there was no love since mother and father always fought. He disregarded the suggestion that love seemed rather important to him and produced another version of "Arne's love." He then agreed that he was not loved, said that love was what he wanted, and volunteered to produce something for every room in the Child Guidance Clinic. He said there were five members in his family, including a talking parrot, but specifically excluded the younger sister, stating that he was the only child. During the session the patient appeared to be testing out the therapist, making a bid for his love and attention, and indicating how lonely and unloved *he* was.

At the next visit, the patient brought the therapist an orange. He then spent most of the time drawing animals for the therapist and adding abdominal appendages which he first called "the tail," then later "the tip," and finally "the tits." There was some discussion of masculine-feminine differences, but the patient blocked rather readily. In the next period he further amplified his feelings about his family by drawing a heart with an arrow through it, printing "happy" beneath it. He said this represented the whole world and also his family, both of which he wished to be happy. He then drove a toy rubber knife through the heart until he had torn it up completely, stating that this was what

happened when there was a fight in the family. There followed a discussion of how the children of a family felt when the parents fought, and the patient was finally able to admit that aggressive attitudes on the part of the parents severely threatened the security of the children. The patient then carved the initials USA on the back of one of the playroom chairs, and when it was suggested that it would be wise to stop since this would eventually come to the attention of the General, he launched into an attack against "the old General who is always putting his nose into things," which increased in feeling until the patient was running around the room, shaking his fist and swearing. It was suggested that Generals might be like fathers and the patient agreed, adding that they were even more like mothers, "always minding somebody else's business," etc. After verbalizing and acting out tremendous amounts of hostility the patient printed a sign stating "Mind your own business," and hung it outside the door; then, in a triumphant frame of mind, he made his mother come back to see it. In the following session the patient became physically aggressive toward the therapist and when it was pointed out that this could not go on, the patient hit himself over the head with his toy revolver. It was suggested to him that he must often hurt himself when he felt like hurting others. He said this was true, and then described how he wished he were a magician so that when his parents came to whip him, he could turn the tables and give them a merciless drubbing. Unfortunately he was small and unimportant and his wishes never mattered. The therapist agreed that he could not do this, but suggested that it was sometimes as good to talk out one's feelings and the patient agreed. In the next several interviews, the patient continued to act out aggressive feelings toward the therapist, gradually developing a more realistic conception of the limits to which he could carry this. He could now express his feelings of hostility and frustration over losing checker games and was able to state further that he realized he lost because of his own inexperience compared to the therapist's; that eventually he would get better and might win. He was complimented both on the improvement in his playing technique and on his more realistic and mature attitudes. By the end of the thirteenth session it was felt that the patient deserved a temporary cessation of therapy since improvement had been so marked. At that time he had not had a single attack of asthma for approximately seven weeks.

The mother reported marked changes in the boy's personality, with enthusiastic socialization, a normal amount of small boy aggressiveness, and an increasingly happy relationship between father and son. She was also pleased that his work in school had shown marked improvement. Her own attitude had shown definite changes. She had become relaxed and relatively free of anxiety concerning the patient. She felt that the patient was capable of proceeding at his own rate and let him do so. The result was obvious improvement in the mother-son relationship. An over-all improvement in the family atmosphere had occurred along with symptomatic improvement in the boy.

In an attempt to detemine whether there was any noticeable change in the level of mental function and potential over that indicated by the first set of

psychometric examinations, a second group of tests was given to the boy one month following cessation of therapy. It is interesting to note that the Stanford-Binet findings were astonishingly consistent in their demonstration of a functional age level three years below the stated age. Arithmetical conceptions, practical judgments, visual-motor coordination, and language comprehension all continued to show retarded developmental status. On the other hand, the Rorschach data delineated basic intellectual qualities which were well above average and near the adult level. There was good productivity, ability to maintain attention, abstract conceptualization, and adequate intellectual control. The performance intelligence examination (Goodenough) reflected marked growth in use of abilities during the therapy period. Since school work was also up to average or better in the later stages following therapy, and his reading was also adequate for his grade, these, along with the Goodenough scale and the Rorschach, would tend to refute the Binet findings of continued borderline intelligence. The psychologist made the suggestion that the possiblility of organic dysfunction, especially convulsive disorder, should be explored. Electroencephalogram was normal and there was no evidence of any organic lesion. Final impression was that the boy was still emotionally immature for his age and approximately at the intellectual level as indicated by the Binet rather than the Rorschach. In the nine months during which the patient has been periodically followed since termination of therapy, he has been completely asthma-free, save for one brief episode during the early pollen season.

Conclusion.—This 9-year-, 9-month-old patient presented a problem of severe bronchial asthma associated with moderately severe personality disorder. His asthma appeared directly related to a combination of definite allergic diathesis, plus a disturbed emotional situation in the family environment, manifested primarily by poor parent-child relationship. Over a relatively short period of therapy, during which the boy was seen once each week for thirteen weeks by the psychiatrist, and the mother for half-hour counselling periods at similar intervals by the psychiatric social worker, definite improvement occurred in family interpersonal relationships as well as in the over-all personality picture of the boy. The complete clinical remission of the patient's asthma, with the exception of one brief episode during the early pollen season, would seem to indicate that psychogenic factors were operating as an important trigger mechanism in setting off this patient's attacks of bronchial asthma.

Dr. McKhann.—We have all seen patients who demonstrated the importance of psychogenic factors in the precipitation of allergic manifestations. I am reminded of a young woman who has had eczema since infancy. She had an apparently happy girlhood and during this interval her eczema was minimal. Shortly after her marriage her eczema became generalized. Remissions of her eczema were then directly correlated to the tranquillity of her domestic life. She eventually was divorced and her eczema subsided.

Dr. Russell J. Blattner (Civilian Consultant in Pediatrics).—I am most impressed with the cooperation evident between the Pediatric and Neuropsychiatric Services at Brooke General Hospital. I concur with Dr. McKhann's

statements that extreme care must be exercised to eliminate organic disease before ascribing the cause of a patient's complaint to such things as family conflict. One of the chief objectives of giving pediatric residents experience in the Child Guidance Clinic is to make them aware of potentially dangerous family situations. A pediatrician so sensitized by experience in Child Guidance Clinics can transfer the knowledge thus gained to the broader fields of preventive psychiatry in daily practice.

DR. SIDNEY KALISKI (Civilian Consultant in Pediatrics).—Referring to the case of ulcerative colitis, I would like to comment that, although there is a well-established component of psychogenic overlay, it is a little difficult to accept this case as being of purely psychogenic origin, inasmuch as the patient has had, (1) a clear-cut case of Salmonella enteritis, and (2) a considerably elevated sedimentation rate. It is only natural to assume that environmental factors contributed to the prolongation and aggravation of his colitis. It would, nevertheless, be intellectually imprudent to present this case as being due to psychogenic factors alone.

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Psychologic Aspects of Pediatrics

COUNSELLING SERVICE FOR PARENTS OF YOUNG CHILDREN

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IN NOVEMBER, 1947, Group Health Association, a cooperative medical group operating as a group clinic, established an experimental mental hygiene counselling service in conjunction with its pediatric department. The purpose of the service is to provide short-term guidance on problems connected with the usual conflicts between parents and children. The service uses preventive techniques in the field of mental health to resolve minor difficulties and thus avoid the development of major problems. It does not attempt to handle cases where there is need for more intensive treatment.

This report on the first two years of operation of the counselling service is given to encourage further development of this type of service elsewhere.

As pediatric practice has developed from concern primarily with treatment of diseases to comprehensive care with emphasis on prevention, pediatricians have found themselves increasingly occupied with problems of emotional adjustment of parents and children. At Group Health, as elsewhere, many office and telephone conversations with parents deal not with physical illness but with such problems as the struggle at bedtime, the child waking at night, feeding difficulties, temper tantrums, excessive shyness, thumb-sucking, masturbation, head-banging, rocking, and so forth.

Even a family that seems to be getting on well may accumulate many relatively minor troubles, which together interfere seriously with well-adjusted living. These difficulties may build up unnoticed for a long time, sometimes from the birth of the first child, until the warning signal of the symptom comes out in bold relief.

The parent whose child has developed a behavior problem all too frequently worries about whether the child is normal. This fear frequently engenders an attitude of watchfulness and worry which is sensed by the child, and which leads to an accentuation of the behavior problem or gives rise to a new one. Most families have this experience during the growth and development of their children. Few indeed are the families which cannot at some time benefit by the advice from a trained consultant in child behavior problems.

The pediatrician is in a singularly favorable position to learn of behavior difficulties that arise early in infancy. The pediatricians on the Group Health staff have been interested in the emotional stresses and strains that beset children. They recognized that there were many problems which could not be handled successfully by the parent, but which, nevertheless, were not serious

From the Department of Pediatrics and Mental Hygiene Clinic of the Group Health Association Clinic.

enough for referral to a psychiatrist. They felt that problems of this kind, if discussed with the parent during the child's earliest years, could be handled adequately by a trained, supervised, psychiatric counsellor, usually in one or, at most, a few interviews. While it might seem simpler to treat these problems in the pediatrician's office, the pediatrician usually lacks the specialized training to help parents expertly and expeditiously.

After much discussion among the staff pediatricians and with leading psychiatrists, psychologists, and psychiatric social workers, a meeting of the members of the Association was called to discuss a mental hygiene consultation service. The members were told at this meeting that "good health depends on more than a sound body and properly functioning organs; it depends also on peace of mind and a sense of security." It was pointed out that many of the medical conditions which cannot be diagnosed are the result of emotional disturbances. The symptoms are nonetheless real. The doctor's responsibility, after he has recognized the cause of a condition to be emotional, is to refer the patient to a person especially trained in this field.

It is still too commonly thought that psychiatric services are indicated only for adults, or for children who present serious behavior problems. Actually, psychiatric work with the parents of very young children who present minor behavior difficulties can be most effective. In the majority of cases such difficulties arise out of some strain or tension in the relationships within the family group, and not from any innate weakness or "cantankerousness." If the cause of the behavior problems goes unrecognized, and the contributing conditions remain unchanged, these experiences may affect the personality of the child permanently. While pediatricians are able to give some assistance to parents, they feel the need for a person especially trained to do parent-guidance work.

After free discussion of these ideas, the Association membership approved the plan for a counselling service in our pediatric program on a cost fee basis, since psychiatric service is not included in membership coverage.

Group Health employed on part time a psychiatric social worker who had had experience in the psychiatric outpatient department of a hospital, in short-term counselling of mothers, and in the adult education field. This "counsellor" saw an average of nine patients in an eighteen-hour week, spending about one-half the time in actual counselling and one-half in reviewing the patient's medical records, recording summaries of her interviews in the medical records, and making referrals and phone inquiries regarding resources. The counsellor was supervised by a psychiatrist, with consultation and diagnostic psychologic studies of the child (when necessary) by a clinical psychologist. Thus a service was made available to patients, under the auspices of their own pediatric service, for dealing with behavior problems which might become serious.

At first referrals were made only by the pediatricians of Group Health, but, as the staff became familiar with the counselling service, referrals were also made by obstetricians, gynecologists, allergists, and internists. Self-referrals have become increasingly numerous. At no time has there been a feeling on the part of patients that they must use the service.

In dealing with emotional difficulties, the pediatricians evolved some effective ways of suggesting to the parents that they use the counselling service. When direct advice failed, or when there seemed to be some reluctance on the part of the parents to consult the counsellor, they could explain that the usual remedies were apparently found wanting in this case, and that it was time to call in the guidance counsellor to help evaluate emotional factors. In other cases they could say that they had examined and re-examined a particular problem from a physical point of view and had found everything normal. Yet the problem was still present, and it would be fruitless to continue along the same line. Therefore, just as in the case of a heart problem, we should get help from a specialist, in this case someone trained to deal with emotional problems. This we could do more easily because the counsellor's advice was directly connected with our pediatric service, and parents were frequently ready to accept trained counselling service at this stage. In fact, at times we were able to say, "This condition in our experience is rarely, if ever, on an organic basis, and the simple tests in this case are negative. It would seem to be more feasible to see the child guidance counsellor first and get her opinion and help. If that proves fruitless, then we can subject the child to an exhaustive study from an organic standpoint." We were surprised to find how many parents were ready to accept this course of action.

Use of the counselling service by parents of children in the 1- to 5-year age group was emphasized for two reasons: the potentialities of preventive work are greater with parents of younger children; and working with the parent, rather than directly with the child, is more productive in the child's infant and preschool years. Interviews were held with the mother or father, or both, but the service limited itself to difficulties in interpersonal relations which were focused on the child.

In an initial statement to the Group Health medical staff, the pediatrician was indicated as the key person for (1) selection of patients who could make best use of the counselling; (2) recording the salient facts in the medical chart for the use of the counsellor; and (3) interpreting to the parents the use of the counselling program.

These three functions were explained to the pediatricians as follows:

1. *Indications for Selecting Patients for Referral to the Counselling Service.*—

In selecting patients to whom counselling service can be of most use, the following kinds of mothers (or fathers) may be considered as indicating their need for this kind of help: the overprotective or habitually anxious parent; the seemingly indifferent or neglectful parent; the severely repressive parent; the parent who cannot accept a child's physical limitations or disabilities; the parent who is overdependent on the physician; the parent who is uninformed about children's emotional development, but indicates willingness to learn.

In general, any parent who feels that he or his child has a problem (even if the physician sees none) is indicating a need for some kind of counselling.

Among the child's behavior difficulties which might, if without physical cause, be considered a good basis for referring the parents to the counselling

service are: feeding (resistance, food fads), elimination (enuresis, habitual constipation), sleep (poor habits or attitudes), speech development (lags or abberations), fears (night terrors, chronic daytime fears), "nervous habits" (nail-biting, thumb-sucking, excessive masturbation), poor social development (excessive timidity, overaggressiveness), relationship to siblings (unusual rivalry), poor relationship to parents (temper tantrums, overdependence), and psychosomatic symptoms. Referral might also be indicated for parents of children who are suffering frustration through chronic illness, mental retardation, or prolonged illness; or of children who are experiencing special turmoils in the environment, such as marital disharmony or death in the family.

It should be borne in mind, however, that unless the parent has some recognition that these symptoms are danger signals and warrant concern, he may be unable to benefit from referral to counselling service, even though the pediatrician may be aware of the need for help.

2. *Recording of Salient Facts Regarding Parent or Child in Medical Record.*—

The physician has a special opportunity to observe behavior as well as physical facts about a child. Noting these observations briefly in the medical record of the child whose parent is referred to counselling service will mean fewer questions to be asked in the counselling interviews and more rapid diagnostic help. The counsellor does *not* see the *child*, and therefore will find it valuable to have the physician's objective observation of the child for comparison with the parent's description.

3. *Interpreting the Counselling Service.*—

The physician can be the key person in successful utilization of the counselling service by his own recognition that the difficulties of the child reflect some conflicts in the parents. He can avoid putting such parents on the defensive by emphasizing that the counselling program is not designed for the mentally ill or the deeply neurotic child, but is a preventive service for the "normal," "average" child and the parent who has some tension or anxiety about his child. In making a referral, it should be made clear to the parent that one counselling session may or may not be sufficient to help him.

At the very least, the service should aid the parent by making it possible to discuss his problem with a trained understanding listener. Discussion in itself often helps the parent see the problem more clearly. Furthermore, the counsellor will try to help the parent to analyze the situation and focus on the basic problems which have precipitated the child's difficulties, in the hope that, as the parent achieves further insight into his personal relationships and needs, the tensions causing the child's behavior difficulties may be released.

It sometimes happens that discussions with the counsellor reveal that a problem seems to call for additional measures, such as the services of a family or children's service agency, recreational guidance, psychologic testing, nursery school placement, play therapy, or other resources. In such cases the parent is helped to utilize these resources. If extensive psychotherapy is indicated, the patient is prepared for and referred to whatever long-term psychiatric resources are available.

Even after the enthusiastic mass response of the Group Health membership and the careful introduction of the counselling service to the patients and physicians, few patients used the service when it was first started. Parents and expectant parents need repeated and individual education in the potentalities of such a program, and need to be encouraged to make regular use of its service, much as they would of routine physical examinations and immunizations. As time passed, however, an increasingly large percentage of parents to whom we recommended the service followed our advice.

After the service had been in operation for two years, we attempted to evaluate its usefulness in relation to the needs of our patients. We found that 318 families had used the service, with a total of 460 interviews. In the first nine months the ratio of families to interviews was almost 1 to 1; in the second nine months fewer families were seen, but the average number of interviews was higher. This was because we found that if the counselling was to be more than a superficial advisory service, more time had to be taken to help the parent evaluate his relationship with the child. As the service develops, it seems likely that more and more patients will be seen several times, although the counselling will still not be allowed to overlap into the field of intensive therapy.

Most interviews were with the mother, but in 80 of the 318 families at least one interview was with father and mother, or father alone. The ages of the children discussed ranged from 3 months to 17 years, with the great majority of preschool age. The range of problems brought was varied, including all the categories of symptoms mentioned in our prospectus (just quoted) to the physicians. Summaries of different types of problems brought to the counselling service are presented below, with some indication of the counsellor's function in each.

Mrs. A. was referred by her pediatrician because her little boy, Johnny, aged 6 years, a healthy and attractive child, was excessively timid. When the mother discussed the child's difficulties with the counsellor, it became apparent that she had herself been a painfully timid child and young person, dominated by controlling parents, and that these elements were entering into her relationship with her child and her child's excessive shyness. Two subsequent interviews served to clarify for Mrs. A. her early resentment of her parents whom she had punished by her own shyness. A Rorschach test was made of Johnny, and Mrs. A. became aware of the ways in which she was repeating her parents' patterns with her son, with the result that he also took refuge in the symptoms of shyness. As she was able to release the child from the need for his shyness, Johnny began to grow more independent.

Mrs. A. also used the counselling service to discuss her daughter's social and school adjustment. The father came in for one interview to see how he and the mother together could carry out plans for helping both children. Both parents feel free to utilize the service every few months to sustain the gains they feel have been made.

Mrs. B. and her husband have had only one interview so far. They were referred by two pediatricians because of their 5-year-old son Joel's possessive

jealousy of their 2-year-old son Mike, and because of his recurrent allergic reactions. They were also referred because of Mike's violent resistance to mealtimes and sleep times. In the counselling interview, it developed that the two children had been handled entirely differently, each according to the extreme of the particular "psychologic style" of the time. Joel had been on a rigid schedule with much pressure and high expectations by his parents. Mike had been on a demand schedule with no modifications, demanding the attention of the rest of the family to the point where he now insisted on the family's attending him in bed for an hour and one-half before going to sleep each night, and at intervals several times each night.

Mrs. B. was now pregnant with the third child, and beginning to rebel against the demands she had been giving in to so compulsively. She was also beginning to worry about Joel's submissiveness. This concern, plus Mr. B.'s insistence that his work was suffering from lack of sleep, enabled her to follow the counsellor's suggestion that Mike be "told off" gently but firmly, and quietly left alone at night, and that he no longer be needled and bribed to eat at the family mealtime.

Mike had begun to go to sleep promptly and to eat small and sufficient amounts on his own initiative. But the door to real mental health in this family has been opened only a little by these alleviating suggestions. The mother needs longer and more basic help in order to understand and mitigate her extreme and compulsive reactions to both children. She has been asked to return for further discussion (and probable referral to a child guidance clinic) after the birth of the third child.

Another type of service is typified by two consultations with Mrs. C., a primipara 30 years of age, who had been a successful professional person. In discussing her 3-month-old child with the pediatrician, she gave vent to many and severe anxieties about the minutiae of caring for her child, and she telephoned the pediatrician many times each week about crises which did not materialize. Here the counselling service was utilized as a vent to free-floating anxieties, but also to give Mrs. C. some understanding of the reasons underlying her "alarums and excursions." With this enlightenment and some discussion in advance of what developments she might expect in the next few months of her child's growth, she found she did not need to look so often for reassurance from the doctors.

The counselling service was utilized in a different way in the case of Mr. and Mrs. D., whose 8-year-old Mary had a brain injury and suffered from mental retardation, with some behavioral manifestations which were difficult but not serious enough to call for commitment to an institution. These parents needed help in understanding and accepting their child's limitations. Over a period of two years in which they used the counselling service at about monthly intervals, they progressed to the point where they could deal with such questions as home management and helpful disciplines and routine for Mary's schooling, utilizing special recreational and educational resources, and helping

the other child in the family in his adjustment to Mary. This kind of counselling with both mother and father gave them a perspective in adjusting to a limited child and in helping her make the most of her capacities.

In the case of Mr. and Mrs. E., the service was used by the alert pediatrician as a link to potentially needed long-term psychiatric care. The pediatrician had been deeply concerned for three years about a 13-year-old boy who was extremely seclusive and oversensitive, felt persecuted, and was making a poor school adjustment. The pediatrician felt this was a preschizophrenic boy, but, although Mrs. E. was much concerned, Mr. E. rejected the idea of any psychiatric help for his child on both intellectual and financial grounds. When the counselling service was established in Group Health, however, both parents were willing to accept referral to it. In the course of discussion, the parents finally recognized the need for emotional help for the child, and accepted a referral to the child guidance clinic, which was able to make a definite diagnosis and help the parents plan a treatment course.

In an attempt to obtain an evaluation of the counselling service from the patients themselves, questionnaires were sent out to 171 families seen in the first eight-month period of the service. Seventy-eight questionnaires were returned, of which twenty-nine indicated that the service had been very helpful, forty-one that the service had been helpful to some extent, and eight that the service had not been helpful at all.

It may never be possible to evaluate the benefits of a mental hygiene program in percentages, as one would a new drug. However, in our own evaluation of the work of the counselling service, we are able to perceive certain areas of greater and of lesser effectiveness, within the limits set up for the service:

1. In general, such problems as chronic enuresis and psychosomatic symptoms presented etiologic factors of such depth or complexity that the counselling service usually served only as an outlet for accumulative parental anxiety or resentment, giving some temporary relief, or as a bridge between the pediatrician and more intensive psychotherapeutic resources, such as child guidance clinics or psychiatrists. In explaining the need for further help, the physician found particular value in being able to refer a patient who persisted in thinking of a psychomotor symptom as purely physical in nature to a trained person who could give some understanding and acceptance of the emotional factors involved.

2. In situations where one major area of anxiety, such as concern about the young child's eating, sleeping, toilet training, or parental or social relations was involved, parents frequently benefited from authoritative, practical guidance in the management of the child, combined with some degree of insight into the reasons for their own tensions about that particular area of behavior. At its best, this kind of insight helped the parents to be less anxious, more enlightened as to the source of the friction, and therefore able to relieve pressure on the child, thus mitigating the symptoms. It helped the parent in some cases just to recognize the fact that he had a problem. Many of these parents then

stated to the pediatrician that they could handle the problems satisfactorily or were no longer bothered by them. At times, this carried over into areas not discussed with the counsellor. These self-evaluations were accepted by the pediatricians critically and often with much skepticism. Nevertheless, we saw definite signs of improved relationships between parent and child, greater relaxation, and fewer urgent calls on the pediatrician for recurrent "crises."

3. Situations which appeared particularly well suited to short-term consultation were those involving specific adjustments, such as acceptance and management of a child's chronic illness, disability, or retardation, or the planning and adjustments related to parental illness, death, or disharmony.

4. Another area of effectiveness was interviews with pregnant primipara's and with anxious parents of young infants, who were given general orientation regarding the developing child's needs, and some discussion of the particular strains or tensions these parents brought to parenthood.

5. Although the use of the service by parents of children aged from 1 to 5 years was emphasized, it was found useful to allow initial use of the service by any parent who so desired. This probably cut down on the number of interviews which could give appropriate help within the limitations of short-term counselling, and increased the number of interviews which served as intermediary referrals to more intensive psychotherapy. However, we felt that this broad use of the service was particularly helpful from the educational point of view in introducing parents to the use of guidance facilities as an acceptable and common preventive practice, not indicative of "total failure" on the part of the parent.

6. The inestimable educational value of a counselling service showed itself in a definite reorientation, a shift of thinking on the part of many parents, from "the child is doing thus and such. I do not like it. What can we do to change it?" to "The child is doing thus and such. I wonder why he needs to do it," and even, "Why does it annoy me so much?" This changeover from simply trying to find a mechanism for dealing with a particular problem to trying to understand the dynamics of behavior of oneself as a child as well as in the child is often a subtle one, but very gratifying to behold. In developing this point of view, we believe that pediatricians, through a counselling service, can make a substantial contribution to the mental health of their young patients.

Finally, it seems to us that groups of pediatricians in private practice could find it feasible to set up similar plans through which they could refer parents of young children to the resources of a well-trained and supervised psychiatric social worker.

Comments on Current Literature

TORULA MENINGOENCEPHALITIS

THE remarkable success now being experienced in the treatment of infections of the central nervous system by means of chemotherapeutic and antibiotic agents has served to focus the attention of clinicians on those patients with central nervous system infection who fail to respond to treatment. Torulosis of the central nervous system is a notable example.

Infection of the central nervous system with *Torula histolytica* (*Cryptococcus neoformans*) has been recognized for more than fifty years and has been reported from all over the world. Voyles and Beck[1] reviewing the subject in 1946, tabulated 108 cases reported in the literature up to that time. In the June, 1950, issue of the *Annals of Internal Medicine*, Mosberg and Arnold[2] review the literature since 1946 and add sixty-four new cases to the recorded incidence including five of their own. While torulosis of the central nervous system is primarily a disease of adults, their survey revealed that eleven cases occurred in children under 10 years of age and sixteen in the age group from 10 to 19 years. The rest of the cases reported were in adults: thirty in the age group, 20 to 29 years; thirty-two aged from 30 to 39 years; thirty-three cases from 40 to 49 years; thirty-five cases from 50 to 59 years; nine cases from 60 to 69 years.

The diagnosis of torulosis is difficult because the disease presents a protean neurologic picture. The diagnosis cannot be made on the basis of clinical signs and symptoms alone, since the clinical manifestations may resemble those of pyogenic, syphilitic, tuberculous, or benign choriolymphocytic meningitis. Torulosis of the central nervous system may be confused readily with brain tumor, subarachnoid hemorrhage, brain abscess, encephalitis, or subdural hematoma. The febrile course is usually but not invariably characterized by low-grade fever; however, the temperature may be normal. Hematologic studies and even spinal fluid findings may be very inconstant, and are of little diagnostic value. The authors state that clinically one should be aware of this disease at all times, and that torulosis should be suspected whenever an unexplained cerebrospinal fluid pleocytosis is present.

While the spinal fluid findings may not be pathognomonic of torulosis, certain features suggest the diagnosis. The cell count is usually elevated with a high lymphocyte count, although polymorphonuclear leucocytes may predominate. As a rule, the spinal fluid sugar is diminished significantly, and the spinal fluid protein is almost always elevated. Definite diagnosis ante mortem can be made by proper examination of spinal fluid samples for the presence of torulae, and particularly by proper culturing of the spinal fluid. The authors suggest search for torulae in repeated samples, repeated cultures on Sabouraud's medium, and that cultures be followed for a minimum period of one month. They emphasize the practical point that one or more negative cultures do not exclude the possibility of torulosis.

The detailed analysis of their own five cases and their excellent analysis of cases reported in the literature bring out several significant clinical points. First, clinical awareness of the disease; the authors believe that cases are missed because the clinician does not have this diagnosis in mind. Secondly, their studies reveal that torulosis may present an extremely bizarre clinical picture and may be remarkably chronic in nature; in their cases, for example, the

clinical course extended eight months in one instance, nine weeks in another, thirty-eight months in another, seven months in the fourth case, and three months in the fifth case. While the symptoms and signs presented by these patients definitely focused attention on the central nervous system, the exact etiologic diagnosis could not be made unless the organism was observed in the spinal fluid, and particularly unless the organism was cultured from the spinal fluid. These authors emphasize also that while the eventual outcome of the disease is practically always a fatal one, there is great variation in the severity and the length of the clinical course between the onset of the initial symptoms and exitus.

In three of their five cases neurosurgical intervention had to be considered, and this possibility is emphasized likewise in the cases reviewed from the literature. In their first case the ante mortem diagnosis was missed mainly because of dependence on the report that the blood serum showed a high titer of antibody against the virus of lymphocytic choriomeningitis. No report of increasing antibody level against this virus during the clinical course of the illness was obtained, however, and it was only at the time of autopsy that the correct diagnosis was made. The authors are of the opinion that the clinical diagnosis was missed because torulosis was not suspected.

The second case was noteworthy in that the clinical findings suggested strongly the diagnosis of frontal lobe tumor, and the third case was of interest in that a cerebellar tumor had been suspected on the basis of clinical signs. At autopsy no evidence of torulosis was found in this case, although there had been ample verification of the clinical diagnosis by culture of spinal fluid samples carried out ante mortem. The meninges in the lumbar region were markedly thickened, a moderate internal hydrocephalus was present, and violin-string adhesions were noted in the fourth ventricle. The importance of this case is obvious in that apparently the fungus infection had been brought under control, and possibly even eradicated, but the residuum of the infection caused difficulty. Whether neurosurgical intervention might have helped in this case was considered seriously by the authors. The last case was remarkable in that autopsy revealed a generalized moniliasis in addition to the diffuse torula meningoencephalitis. *Monilia albicans* was cultured from the brain as well as from the granulomatous lesions in the lungs.

Mosberg and Arnold describe in considerable detail their various efforts at therapy. Many therapeutic procedures were undertaken, and in three of their cases alkalinization therapy was used. In Case 3 the patient was placed on the following treatment schedule: restricted chloride diet; sodium bicarbonate orally, 80 gr. per day; sodium bicarbonate intravenously, 7.5 Gm. per day; and citrocarbonate orally, 12 dr. per day. The dosage was increased gradually until she was receiving sodium bicarbonate, 400 gr. per day, orally; sodium bicarbonate, 28 Gm. per day, intravenously; and citrocarbonate, 16 dr. per day, orally. On this regime the carbon dioxide combining power rose to a level as high as 63 volumes per cent, averaging 59 volumes per cent, and the spinal fluid pH rose from an initial reading of 7.0 to 7.85. In this particular instance the patient seemed to improve under the alkalinization therapy.

In Case 4 similar alkalinization therapy was administered, and while the patient appeared clinically better, the ultimate results were equivocal. In Case 5, likewise, the alkalinization therapy was tried, but the results were not clearly beneficial.

The authors include an excellent review of therapeutic measures employed by various clinicians in the cases reported, and in each instance a concise evaluation of the results is given. The only conclusion which can be drawn from the therapeutic results reported is that no treatment has proved successful in

torula infections involving the central nervous system. These authors also suggest that torula infection of the central nervous system is not so rare as most clinicians tend to assume. They point out that since 1946, sixty-four cases of torulosis of the central nervous system have been reported in the literature as compared with the 108 cases reported in the literature up to 1946, and explain the increased incidence on the basis of more accurate laboratory diagnosis of the condition. They emphasize again that the chief error in diagnosis lies in lack of awareness of the disease. They urge strongly that routine cultures of spinal fluid be made on Sabouraud's medium and observed for a period of one month.

A recent favorable report by Christie and his associates[3] of the treatment of histoplasmosis with ethyl vanillate is of special interest in this connection. Response of patients with histoplasmosis to ethyl vanillate has been so encouraging that it would seem hopeful that other fungus diseases might respond to this therapeutic agent. Clinical trial of this new therapeutic agent in the treatment of torulosis of the central nervous system seems definitely indicated.

RUSSELL J. BLATTNER.

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Correspondence

London, July, 1950.

I imagine that at the present time what is of most interest in this country to paediatricians in the United States is the way the National Health Service is working out, and how it is affecting paediatrics in England.

It is, of course, far too early to do anything but make tentative remarks and give some idea of how things appear at present; with the introduction of a scheme of such magnitude it is likely to be eight or ten years before any final conclusions can properly be arrived at.

Broadly speaking, it seems, at the moment, that the family doctor in general practice is overworked, and is being further separated from hospital practice than before. At the present rate of remuneration he must, in order to make an adequate living, have on his list so many patients that it is almost impossible for him to do the best work It therefore comes about that many general practitioners, especially those working in urban or suburban districts, who are used to carrying out high-class practice, taking time over each case and keeping full case notes of each patient, are penalized. This results in general family practice losing much of its attraction to the best men and women, and there has been a great urge for them to try and obtain special diplomas and higher qualifications with a view to qualifying as specialists. This trend to some extent underlines a feeling that is growing up, and is greatly to be deplored, that there is a widening gulf within the profession between the general practitioners, who are as it were becoming the underprivileged section of the profession, and the consultants. It is recognized that the training of the latter must of necessity be longer, and that therefore in the end they should reap somewhat higher rewards, but it would be a bad thing if general practitioners should come to be put in the position of having to carry out, without adequate facilities and with constant pressure upon their time a mass of routine work without the full opportunity of being guide, philosopher and friend to their patients, as they have been up till now. The cooperation between the two sections of the profession which has always existed in the past must continue, and things must be shaped so as to avoid a drift apart.

The hospital and specialist service is working smoothly on the whole, and little difference is, superficially at any rate, noticeable in hospital practice, except that the number of patients attending the out-patient sessions has not unnaturally increased. The basic remuneration for consultants has been settled, but the special awards, based on the recommendations of a committee especially set up for the purpose, have not as yet been allotted. These so-called "merit awards" were designed to attract into the sphere of consulting practice the most able men, and were to be paid as increments to the basic remuneration of those consultants who were deemed by their status, past work, medical record and teaching ability to merit such increased remuneration. The committee finally responsible for making these awards has had no easy task, and in fact has not yet completed its work although the National Health Service has been in existence now for two years. The awards when made are to be retrospective to the 5th July, 1948, and not unnaturally consultants are getting a little restive at the delay there has been in this matter.

The enormous expense of the Service, and the increase of expenditure above the original estimates, is very striking, and somewhat alarming.

So far as paediatrics is concerned there is nothing special within the Service calling for comment. It was thought that the number of trained men suitable for consultant posts might be insufficient, but any such difficulty is being overcome, and a supply of younger men with proper training is proving sufficient for present needs.

Perhaps the greatest trouble of all, in our hospitals at present, is the scarcity of trained nurses; for this the Service cannot, however, be blamed, but it is a matter of much concern to us.

Some publicity has been given over here in the medical press to remarks made in the *Reader's Digest* by Mr. Harold E. Stassen, of the University of Pennsylvania, on our National Health Service, and to the reply to these by Sir Heneage Ogilvie, Surgeon to Guy's Hospital. There is no doubt that at least some of Mr. Stassen's conclusions are not justified, and it is wrong to suppose that at this relatively early stage in its history the Service is in anything but a formative stage. As Sir Heneage quite rightly points out, "The really vital question is not whether the State takes part in the future development of a medical service, but, if and when it does so, what part it will take." This surely is the really important question and one which confronts the American medical profession today.

Seven years ago the British Paediatric Association began a study of neonatal mortality. It was soon realized that the study would be more profitable if undertaken in collaboration with the Royal College of Obstetricians. A joint committee was formed with Sir Eardley Holland of the Royal College as Chairman and Sir Leonard Parsons of the British Paediatric Association as Deputy Chairman and a report, approved by the Executive Committees of both organisations, has been drafted by Professor T. Jeffcoate and Professor Norman Capon. It forms another of the series of Ministry of Health reports on public health and medical subjects. The report is entitled "Neonatal Mortality and Morbidity," and was published in 1949 by His Majesty's Stationery Office, London. It is a most thorough, careful and excellently documented piece of work. On this account it seems important that it should be brought to the notice of all paediatricians.

Reference has been made in previous letters to the subject of food and health in Britain, and it is therefore worth mentioning that a committee of twenty experts, under the Chairmanship of Lord Horder, M.D., was set up in October, 1947, for the purpose of examining the whole question of nutrition in this country, and of preparing an authoritative report, with particular reference to the adequacy of the wartime and postwar diet. Its report has recently been published, and must be regarded as an important contribution to the literature of nutrition. The main committee set up four subcommittees to deal with various aspects of the subject. The findings of the Committee indicate among other things that during the last few years the population has been consuming enough food to meet nutritional requirements, and that a proportion of the population is certainly enjoying relatively better food today than formerly.

The British Paediatric Association extended an invitation to Swedish Paediatricians, who had kindly entertained many of us at their meeting in Sweden in 1948, to come over as our guests for our own annual meeting in 1949. About thirty accepted our invitation, and we were delighted to have them at our meeting, which proved a great success. The papers were of a high order, and many were contributed by our Swedish guests; they have been reported in the *Archives of Disease in Childhood*. The senior Swedish Paediatrician, Professor Lichtenstein, delivered a lecture on diabetes in childhood, and gave an interesting account of treating children suffering from this disease on a "free diet."

In November, 1949, the British Paediatric Association held a joint meeting with those groups of the Society of Medical Officers of Health who work in paediatrics. This took place in London at the British Medical Association House. This is the first time a meeting of this sort has been arranged, and it afforded an opportunity for a valuable interchange of views between those working in diverse fields, all of whom, however, were primarily engaged in paediatrics.

We are now looking forward to meeting many of our friends and colleagues at the International Paediatric Congress in Zurich at the end of this month, but currency restrictions are such as to make it rather difficult for us in this country. This factor may unfortunately limit the number of British Paediatricians who are able to attend.

KENNETH TALLERMAN.

News and Notes

Dr. Lewis K. Sweet died Sept. 25, 1950, at his home in Falls Church, Va. For a number of years he was head of the pediatric division of the Gallinger Hospital in Washington, and had recently resigned to accept a research position with the National Institute of Health at Bethesda, Md.

Dr. Gilbert B. Forbes, associate professor of pediatrics, Washington University Medical School, has been appointed professor of pediatrics at Southwestern Medical College of the University of Texas at Dallas, Texas.

Dr. John M. Adams, associate professor of pediatrics at the University of Minnesota Medical School, has been named chairman of the department of pediatrics at the new medical school being organized at the University of California in Los Angeles.

Dr. Harry B. O'Rear, Durham, N. C., was named as professor and head of pediatrics at the Medical College of Georgia, Augusta, Ga.

Dr. Fred G. Burke, assistant clinical professor of pediatrics, has been appointed professor of pediatrics at the Georgetown University School of Medicine.

Dr. Einor H. Christopherson of San Diego, Calif., has been appointed Executive Secretary of the American Academy of Pediatrics to succeed Dr. Clifford Grulee who will retire July 1, 1951. Dr. Christopherson was graduated from the Washington University Medical School in 1925. After pediatric training, he entered private practice in San Diego in 1930, and was certified by the American Board of Pediatrics in 1934. From 1942 to 1946, he was in the Army Medical Corps, retiring with the grade of Lieutenant Colonel. Part of his service was with the Service Especial de Saude Publica in Brazil, and in 1945 and 1946, he was Assistant Director of the Division of Health and Sanitation in the Office of Inter-American Affairs in Washington.

The second Maurice Lamm Blatt Memorial Fund lecture was given on Oct. 9, 1950, at the Medical Amphitheater of the Cook County Hospital by Dr. John Caffey of New York, who spoke on "Infantile Cortical Hyperostosis and Vitamin A Poisoning."

A continuation course in Child Psychiatry for pediatricians and physicians will be presented at the Center for Continuation Study at the University of Minnesota Nov. 27 to Dec. 1, 1950. Dr. Ralph D. Rabinovitch and Dr. John Waterman will participate as lecturers and group discussion leaders. Dr. Reynold A. Jensen, Head of the Child Psychiatry Service of the University of Minnesota, is in charge of the arrangements for the course and will also act as lecturer and group discussion leader.

For some months the Department of Pediatrics of Marquette University School of Medicine (561 N. 15th St., Milwaukee 3, Wis.) has been publishing each month a mimeographed list of current pediatric references. The September 15 issue contains references to journals appearing as recent as August of this year. Each number contains about ten pages which may be filed. Dr. A. B. Schwartz is the editor, and references are to pediatric material in American and foreign journals. At present the mailing list amounts to 1,200. There is no subscription but voluntary gifts to support the publication are received.

At the annual meeting of the Section of Pediatrics of the American Medical Association in San Francisco on June 29, 1950, the following officers were elected for the coming year: Chairman, J. B. Bilderback, Portland, Ore.; Vice-chairman, James B. Stone, Richmond, Va.; Secretary, Wyman C. C. Cole, Detroit. Dr. William Weston, Sr., was elected to the office of delegate with Dr. Julius Hess as alternate. Dr. Thomas Mitchell was placed in charge of the Scientific Exhibit, and Dr. Hugh Dwyer, custodian of the Abraham Jacobi Fund.

Book Reviews

Psychological Problems in Mental Deficiency. Seymour B. Sarason, New York, 1949, Harper & Bros., 366 pages. Price $5.00.

This small but comprehensive book is probably the most thorough coverage of theories and practices in the specific field of mental deficiency. The book has material of great value for the pediatrician who is likely to encounter such problems in his everyday practice. The author discusses diagnosis, offering usable criteria of mental deficiency and brain injury, and giving special attention to those types most frequently dealt with by the pediatrician. The incorporation of case history material and suggsetions for therapy, especially the handling of the parent-child relationship, should be of both interest and practical value. The author has selected and organized his material well, and has made a long "over-due" contribution.

S. R. WARSON

Child Development. Elizabeth B. Hurlock, New York, 1950, McGraw-Hill Book Company, Inc., 669 pages. Price $4.50.

This second edition, deleting material related to adolescence, places its entire emphasis on the childhood years, discussing many of the problems frequently encountered by the pediatrician and all who work with children. The material is presented in a textbook fashion, is well illustrated, and partially concerns itself with motor, speech, emotional, social, and moral development. Three new chapters, Family Relationships, Childhood Interests, and Personality, have been added.

S. R. WARSON

Health in the Schools. A Manual of the School Health Program. Departments of Education and Public Health of the Commonwealth of Massachusetts.

This loose-leaf manual of the school health program of the State of Massachusetts was prepared by a group of specialists in the field of school health as a reference guide for administrators, medical officers, and nurses. It outlines and discusses briefly the services, personnel qualifications, and personnel functions as established in Massachusetts. Such matters as environment, health education, disease control, medical examinations, and testing are briefly but completely discussed. It is an excellent job of codification and the school health program in Massachusetts could be profitably studied by administrators in many other states. It is the most comprehensive and practical exposition of school health the reviewer has seen.

Parents Must Be Flexible. Margaret Halmy, New York, 1950, Stephen Daye Press, 127 pages. Price $1.95.

There is seemingly no end to the publishing of books telling how to bring up children. Among the authors are pediatricians, child psychologists, "child experts" (whatever that term may mean), and some who are just "writers." Some we feel are by spinsters who have never faced the problems of a child in the house hour by hour, day by day. Some are pedantic and involved, while others are cocksure and tell just what to do on any and every occasion. Some exploit this or that current psychologic theory, while others are merely eclectic rehashers. We have always had a lot of sympathy for the perplexed young parent who tries to do a good job for her child by following the directions, for they are often quite contrary if she reads several books. So many have been published recently that the Editor opens them with reluctance, trying to decide if they are worth reviewing for JOURNAL readers, and, if so, who he can inveigle into reading and reviewing them.

A few nights ago he opened one and quite unexpectedly found himself chuckling, and it held his jaded interest until he had read it completely through. "Parents Must Be Flexible" is written in a bright, clever way that at first glance conceals the sound wisdom that it contains. Those who feel that the care and development of the child is an awesome subject that admits of no levity and has no humorous side will find the book distasteful, and should avoid it. It is our personal feeling that a sense of humor is probably as essential in the making of a successful parent as the urge and intelligence to read a text on child care and training.

We could find no reference to Margaret Halmy in "Who's Who" or "American Men of Science," and she has no degrees after her name, so all we can tell you about the author, taken from the "blurb" on the cover jacket, is that "she has been in advertising and public relations, and now combines writing with the raising of two children." From the book itself we learn she is intelligent and has a delightful sense of humor, and we would lay good odds that she is an unusually successful parent.

The book consists of some twenty-one brief chapters or themes. Some of the chapter titles will indicate the scope covered and approach to the subject: "Sleep is a sometime thing"; "The inevitability of toilet training"; "Pick a nurse your own size"; "How to handle your doctor"; "Father is a parent"; The truth about grandparents"; "Who needs the discipline?"; "Toys for the child and his parents"; "The origin and species of sitters".

Do not get the idea it is a witty and amusing burlesque, or a satire on child care. It contains about as much good common-sense advice about the problems parents with young children have to meet as we have seen put together. The unique feature is that it is enjoyable to read. Not the least attractive part about the book are the numerous clever and amusing drawings by Barsis illustrating the text. Rarely have we seen a text and illustrations that fit so well together and complement one another. We can only wish there were more books like this available to recommend to parents. One on sex education, for example, would be a gift from the gods.

B. S. V.

The Merck Manual. Eighth edition, Rahway, N. J., 1950, Merck and Co., 1,592 pages. Price $4.50 (Thumb-Index Edition, $5.00).

The new eighth edition of Merck's Manual has been thoroughly revised and brought up to current knowledge. The newer antibiotics, as well as cortisone and ACTH, are included. There are 338 chapters compared with 265 in the previous edition. It is one of the most practical and valuable desk reference books for the practitioner that exists. Its popularity, based on the previous editions, is well shown by the first printing of 75,000 being exhausted by advance orders before publication on June 1. The last edition was published in 1940, and the new edition reflects the tremendous changes which have developed in the medical sciences in the last decade.

Asphyxia Neonatorum. William F. Windle, Ph.D., Sc.D., Springfield, Ill., 1950, Charles C Thomas, 70 pages. Price $2.00.

In a short monograph Dr. Windle presents a discussion of the development of the blood in the fetus and the blood picture of the newborn infant, of fetal circulation and the changes occurring at birth, intrauterine respiration, and fetal respiratory activity. In a final chapter he presents a discussion of asphyxia chiefly based upon his experimental work on guinea pigs. It is an excellent summary of our present-day knowledge and makes a vast amount of physiologic studies available to the obstetrician and pediatrician. The writing is clear and concise. The text is based on a series of lectures Dr. Windle has given on several occasions before educational groups.

Parent-Teacher Series, Bureau of Publications, Teachers College, Columbia University, New York, 1949, Ruth Cunningham, editor; illustrations by Ruth Allcott. Price 60 cents each.

This is a series of attractively printed and illustrated booklets intended for parents and teachers. So far the following eight have been issued:

"Your Child's Leisure Time" by Mildred C. Letton of The Laboratory School of the University of Chicago.

"Understanding Young Children" by Dorothy Baruch, Psychologist.

"Understanding Children's Behavior" by Fritz Redl, Professor of Social Work, Wayne University.

"Answering Children's Questions" by C. W. Hunnecutt, Professor of Education, Syracuse University.

"Discipline" by James L. Hymes, Jr., Professor of Education, State Teachers College, New Palz, N. Y.

"Reading Is Fun" by Roma Gans, Professor of Education, Teachers College, Columbia University.

"Being a Good Parent" by James L. Hymes, Jr.

"Getting Along in the Family" by Jane Mayer.

Each text runs to around fifty pages. As will be noted, the texts are by educators. There is much unevenness in the series. Some are very simple and almost primitive in character, while others smack considerably of the pedagogic attitude. Except that they are in an unusually attractive format, they do not add much to a field that is already well covered.

Food for Little People. Hazel Kepler and Elizabeth Hesser, New York, 1950, Funk & Wagnalls Company, 276 pages. Price $3.75.

This book, a collaboration by a journalist and a dietitian, is a well-rounded manual on the use and preparation of foods for preschool children intended for mothers rather than pediatricians. A good many subjects of child care are touched on which might have been omitted which would make the size of the book a little less formidable. The text recognizes the psychologic aspects of the feeding of young children.

Principles of Human Genetics. Curt Stern, San Francisco, 1949, W. H. Freeman and Company, 617 pages.

Few subjects have had such striking developments as genetics. Professor Stern of the University of California has brought these developments as related to the field of human genetics into a readable text which should be of interest to physicians. Medical literature and knowledge has been amply drawn upon, but the text is fundamental in character rather than an exposition of the medical aspects of genetics.

Editor's Column

TRAINABLE MENTAL DEFECTIVES: A COMMENT ON PROGNOSIS

FROM a therapeutic and prognostic aspect, all mental defectives can be classified into two categories: (1) those requiring permanent custodial care, whether at home or in a suitable institution, and (2) those that are trainable and partially educable and who under suitable conditions might eventually be able to achieve a self-supporting status. From data based on admittedly few adequate surveys, one may estimate that the second group, the trainables, make up approximately 75 per cent of the entire number. While other factors play a role, such as the presence of convulsive disorders, crippling conditions, speech defects, and emotional and behavior disorders, it is, in general, the degree of intellectual retardation that primarily determines the category in which a mentally defective child can be placed. On this basis, the trainable group is characterized by a mental capacity that, measured by acceptable techniques of intelligence testing, ranges between the 45 to 75 percentage levels.

From a practical viewpoint, as regards the trainable group, once a diagnosis is made, and the necessary educational and training program outlined, the most pressing, and at the same time, the most difficult question to answer for the parent is, "How will my child differ from the so-called average or normal child when he or she reaches adult life as regards the various factors which determine community adjustment?" Unfortunately, practically all prognostic studies, large enough to have statistical significance, have been confined to children, trained and educated at schools for mental defectives, and exposed to specialized social service supervision for many years following discharge from the institution. While the results of these studies indicate that satisfactory social adjustment is to be expected, there has been considerable question as to their general applicability to the greater numbers of noninstitutionalized defectives who remain at their homes under the supervision of untrained families and without the specialized facilities available in the better institutions. Moreover, institutions for mental defectives care for less than 10 per cent of trainable defectives, and it is unlikely that the immediate future will see any considerable increase in these facilities. A recent study by Kennedy[1] is of interest as regards our understanding of the prognosis of noninstitutionalized trainable mental defectives. So far as I am aware, this represents the first adequately controlled study having so broad a sociological background and involving numbers that should yield statistically significant conclusions. The plan of the study was basically sound and attractively simple. From the 1937 Connecticut census of "social inadequates" a random list of 260 children, born between 1915 and 1925, having intelligence quotients of from 45 to 75, and who were living in a single Connecticut industrial city, were selected. The original intelligence tests had been carried out, not as a routine procedure, but because the child's

behavior and progress in the public grade schools were such as to suggest intellectual inferiority of a significant degree requiring special class treatment. Of the original names selected on this basis, it was possible to locate and study 256 individuals. At the same time, a random control group of approximately 125 average or so-called normal children who had progressed through school without retardation were selected from the files of the same local public schools. The control group were matched as closely as possible with the defective group as regards age, race, sex, nationality, country of birth, and father's occupation. It thus may be said that both groups, experimental and control, were similar in practically every controllable respect except for intellectual status. Specially trained social workers, primarily through personal interviews, obtained all pertinent facts concerning the social and economic adjustment of these 385 individuals whose average age, at the time of the study, was approximately 25 years. School, social, welfare, vital statistics, employment, court and police as well as military records were consulted. All resulting data were then analyzed by statistically acceptable methods to allow for comparison of defective and control groups. The results were unexpected and certainly startling in their implications. When compared with the control so-called "normal" group living under similar social and economic conditions, the experimental "defective" group made a most creditable showing. Some of the important observations made in both groups were as follows:

1. About 50 per cent of both groups had married, at an average age of about 22 years, and at the time of interview, averaged one child.

2. They were employed or self-supporting to an equal degree, and within relatively similar income ranges.

3. Their work habits, including employer ratings, number of job changes and length of time on last job, were within the same range.

4. Their housing and economic status (savings, cars, radios, insurance, telephones, etc.) were relatively equal and satisfactory.

5. Their community experiences (court records, recreational and group activities, and military service) were relatively similar.

In other words, in this community mentally defective children with intelligence quotients of 45 to 75, cared for, educationally, primarily in special classes but without other special provisions for training, were able, eventually, to make a reasonably normal social and economic adjustment in the community on a self-sustaining basis.

How generally applicable are the results of this study to the over-all problem of prognosis of trainable, noninstitutionalized, mental defectives? The following factors must be noted:

1. The children were brought up in families of which over two-thirds of the fathers were factory workers mainly in a semiskilled or unskilled capacity.

2. The town in which the children were reared was relatively small, with limited economic and social opportunities, all of which would tend to minimize any strong competitive spirit in community living.

3. The study was carried out in 1946. Since the average age of the group was about 25 years, their productive economic life covered the span primarily of the war years, when jobs were plentiful and salaries adequate.

4. Most of the retarded children attended special classes. This would indicate an attitude on the part of the local school system toward mental deficiency that might be expected to be beneficial in the over-all handling of the problem during the early school years, and thus minimize the development of emotional and behavior difficulties.

One must conclude that the study was carried out under relatively ideal conditions as regards these retarded children. So beneficial an environment cannot always be expected. Unfortunately, the trainable defective is also found, although less frequently, in families of higher economic status, with parents in professional capacities, living in large cities with their keen competitive spirit, and exposed to a school system that is not geared to the satisfactory care of these children. All these factors tend to accentuate the basic deficiencies of the defective child to the detriment of his emotional and behavioral development. It is difficulties in the latter spheres that so frequently adversely affect the possibilities for acceptable community adjustment.

The knowledge, however, that trainable defectives can adjust socially and economically, under satisfactory conditions, should serve as a stimulus to the proper manipulation of the environment so that conditions as closely approaching the ideal as possible can be attained. Much of these environmental requirements are community responsibilities. These include, among other things, special educational, training, and recreational facilities, employment counselling and job placement. In addition, parent training, combined with the hopeful prognosis that Kennedy's study suggests, should revitalize our approach to the problem.

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REFERENCE

1. Kennedy, R. J. R.: The Social Adjustment of Morons in a Connecticut City. Mansfield-Southbury Social Service Department, State Office Building, Hartford, Conn.